FOOD & DRUG ADMINISTRATION

CENTER FOR VETERINARY MEDICINE

VETERINARY MEDICINE ADVISORY COMMITTEE

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DAY II

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Dr. Hoffsis: I'd like to call the meeting to order. For anyone who has not signed in over here at the desk, I'll ask you to do that please.

We have a fairly tight schedule this morning at least, and anyone who would like to have some comments, we have time for public discussion and public comment, if you'll notice at the various times in the agenda.

So we will have time and the comments aren't too lengthy, we'll have a chance for everyone to have some say.

This morning we're going to begin with a discussion on the issue of prescription versus over-the-counter products. First of all, how the decisionmaking process is conducted. And we'll start with the unapproved products. Dr. Gable.

Dr. Gable: Ladies and gentlemen. The Center has a foolproof technique for deciding whether the drug marketing status should be over-the-counter or prescription. We use a triple-blinded method.

In the Director's office, he has this large dart board. There are just two colors on that dart board. The first blind deals with the color key to the dart board.

He also has two darts, and the color key to them is blinded, so it's blinded twice.

The third blinding comes in, that the fact that the review personnel are never given the keys to the darts or the dart board.

This time-tested method, the triple-blinded method,

has eliminated all arbitrary and capricious acts by Center personnel in deciding whether a drug should be marketed over-the-counter or prescription.

I started off that way because I am well aware that the prescription or over-the-counter status of animal drug products is a subject surrounded by very strong personal viewpoints.

Every intent is made to eliminate personal factors, personal idiosyncrasies, in the decision on whether a drug should be marketed over-the-counter or prescription.

We try to be consistent in our interpretations, with implementation of the Act, amendments to the Act, reglations and policy pertaining to market status of animal drugs.

The specific areas which I plan to discuss are as follows: the background or legal foundation for veterinary prescription drugs. This is very old hat, but I think it's absolutely, absolutely, basic to any understanding of decisions regarding the marketing status of animal drugs.

Secondly, I'm going to talk about factors associated with the animal drug product that enter into our determination of prescription status.

And then the third point, I'm going to give examples of what policy bears on our decision, and a couple examples where the practice of veterinary medicine bears on the decision to make a product over-the-counter or prescription.

Let's start with the first item: background and

legal foundation for prescription. The Food and Drug Act of 1906 had no authority for any restrictions on drugs.

In 1938, the Food, Drug and Cosmetic Act contained no explicit provisions requiring certain drugs be placed on prescriptions. It did recognize drugs might be dispensed on prescription, since 503 of that Act contained labeling exemptions for drugs dispensed under the prescription of a physician, dentist, or veterinarian.

The 1938 Food, Drug and Cosmetic Act, Section 502(f)(1) states that a drug is misbranded unless its label contains adequate directions for use.

Since 1938, the agency has felt that adequate directions for use by lay persons could not be written for some drugs. However, in 1938, for prescription drugs, no directions for use were deemed necessary.

A physician, dentist, or veterinarian, medical background was felt to qualify him to use drugs safely and efficaciously.

This left the druggists on the horns of a dilemma. He had one company marketing products over-the-counter, with complete labeling. He had other companies marketing it with just identifying the ingredient, the amount, and carried a prescription legend.

This was addressed by the Durham-Humphrey Amendments of 1951. The Durham-Humphrey Amendments contained specific

provisions and criteria for placing drugs on prescription. There are two primary points related to the Durham-Humphrey Amendments that must be emphasized.

The legislative history indicates that Congress believed all human and animal drugs which could be labeled for lay use are ineligible to receive the prescription legend. That is, drug products are to be marketed over-the-counter, unless prescription status is necessary. And I'll keep coming back to that time and time again this morning.

The rule is products are over-the-counter. The exemption to the rule are prescription.

Animal drugs were not included in the 1951 Amendments. Congress was of the opinion that a farmer or a person has a right to do what he chose with his property.

This included the right to treat, or even kill, his or her own animals. However, the Senate committee report stated in part, and I quote this because it's typical Congressional double talk.

"Under the committee bill, drugs intended for use under the supervision of a veterinarian will not require a prescription, although it will be possible under Section 502(f)(1) to accept such drugs for use if they are used by or under the supervision of a veterinarian."

So what had we done in 13 years? We just did a complete circle. We muddied the water and accomplished very little, and still have the provision that we might make something

prescription if it's given by or under the supervision of a veterinarian.

The 1969 New Animal Drug Amendments, Section 512 (d)(2), list specific relevant factors to determine whether a drug product is safe for use under the conditions prescribed, recommended, or suggested in proposed labeling.

As I indicated, this concludes my comments on the Act and Amendments to Acts.

Then we get into the regulations. Regulations interpret Acts, more or less in line with the Congressional intent.

Of the regulations, Section 201.105 of the regulations is entitled, "Veterinary Drugs." This regulation provides parameters within which veterinary prescription drugs can be legally distributed.

This regulation is sometimes referred to as the exempting regulation, because it identifies conditions under which prescription drugs may be exempt from Section 502(f)(1) That is, certain OTC labeling requirements are modified to fit the prescription status of the drug.

Next, I would like to talk about factors associated with a drug product in the determination of prescription status.

Safety of the drug to a target issue -- this is not determined solely by the margin of safety. That is, there is no specific level, 3X or 5X, which separates prescription from over-the-counter status.

An example of this would be that we have several products that are approved for use in administration of animal feeds over-the-counter, which given this margin of safety, there's no way that we could permit the marketing of oral tablets of the same ingredient, or even not necessarily the same ingredient, but the same margin of safety, for tablets for use in dogs and cats

You just could not provide for the accuracy of weighing, the splitting the tablets and everything that would be necessary to provide a margin of safety. At least, you would possibly require an additional tablet for every two or three, four pounds of body weight.

The margin of safety of some of the things that they put in medicated feed, over-the-counter, have a very narrow margin of safety.

Other target animal factors include availability antidotes, which may be only available in the veterinary office. The nature and severity of toxic reactions, serious problems due to drug animal reactions, including immunosuppression, and special handling of the animal.

Let me digress and just note for your information that there are no chicken and turkey drugs that are marketed with prescription status.

Safety to man. This is involved with this multidimensional component that includes diseases communicable to man. It includes dangers to persons administering a drug

product, if it's not handled properly. It also deals with the directions reasonably certain to be followed in practice.

The next item is accuracy of the diagnosis. How readily can the diagnosis be made? How much differential diagnosis is involved? Is the condition readily confused with other conditions? Must the signs of the disease be closely monitored? Must adjustments be made to the dosage regimen, such as in digitalization?

Are specific facilities and equipment necessary for accurate diagnosis?

The next item is the nature of the animal drug product. Potential for misuse in animals or man, such as the prostaglandins.

Controlled substances. Obviously, these have been limited to professional sales since the Harrison Narcotic Act in 1914.

Just let me go off again here. It's conceivable that even a controlled substance could be marketed in the feed if in the pre-mix which carried it, it was infeasible or impractical to recover the active ingredient from such pre-mix or feed. We have not had to face that decision, but we have considered it. We weren't sure until we went and checked whether the product we were dealing with was subject to the Harrison Narcotic Act.

New, untried entities. We use this to monitor toxic effects who have proved it in one species, that has been a

history of difficulties experienced with that approval. We have next approval coming up with the second species, with which the limited studies we've done have shown no problems. We would put it on prescription status until we were even more sure that such was the case.

Special handling necessary -- adding a sterile diluent, refrigerations and the like.

Route of administration. IV for horses, dogs and cats, small animals is prescription. Intra-articular, intrathecal, epidural, subconjunctival and retrobulbar administrations are prescription. IP in horses is prescription, stomach tube in horses is prescription. Large volume parenterals in small animals are prescription.

Lastly, some examples of policy and clinical practice that bear on decisions of prescription status.

The Advisory Committee recommended that all synthetic and semi-synthetic penicillins should carry the prescription legend. This policy was based upon the development of resistant Staphylococcus from widespread use. This policy remains in effect.

I want to note that that Advisory Committee, such as yourself, makes recommendations. All policies are set by the man at the other end of the table.

Policy. We have a policy on intramammary products that are labeled for both Staphylococcus and streptococcus infections. If it carries both claims, it has been shown that

that drug is effective for both claims, it's over-the-counter. That's based on the fact that the majority of cases of clinical mastitis are caused by one or the other.

If it would be limited to either Staph or strep, only one, then we would make it prescription, because of the need for differential diagnosis.

Clorsulon, a flukicide recently approved by the Center for Veterinary Medicine. If veterinary practitioners would routinely confirm either by flotation or sedimentation techniques to check for eggs for Fasciola hepatica, prescription status may have been justified on this product.

Practitioners' reports indicate that neither flotation or sedimentation were employed as part of the diagnosis. Blanket administration to cattle in epidemic areas was established by use reports that we've had from the previous five or six years.

An extremely interesting area within the division that I'm in charge of, the Division of Therapeutic Drugs for Food Animals, is deeply involved in the use of drugs for minor species. We have over 30 active projects in this area right now.

I mention minor species because we see the broadest spectrum in regards to state of the art and science related to veterinary medicine anywhere possible.

We see new food animal industries with new diseases. We have seen, for example with alligators, over a period of years make dramatic improvements in both treatment and

husbandry practices and reduce the mortality rate some 90 percent.

This is an industry that's recently developed, where they go, get the eggs, hatch the eggs in incubators of sorts, and control the rearing of this animal under captivity until he is marketed for both his hide and meat.

Some projects that we have under this minor use, the symptomology is such that the people that are coming in to meet with us regarding the disease entity, describe the entity as the tail falls off, or the animal rots. And there is a variable involvement of the clinical practitioners in a number of these minor uses.

The generalization regarding such minor uses is, except for minor ruminant species and minor uses in ruminant species, that is, it will be difficult to justify prescription status for the other minor uses that are pending at this time.

Conclusions. The three main points I want to leave with you this morning -- first, the decision on prescription or over-the-counter marketing status is complex.

Two, OTC status is the rule; prescription is the exception to that rule.

Third, the Center does give thorough consideration to prescription or over-the counter status. Our deliberations are always fair and equitable, and generally we have been consistent.

Center personnel are like an umpire or referee. Our decision, our calls on these must be consistent.

Ladies and gentlemen, thank you for your attention, and I'll be followed by Dr. Andrew Beaulieu.

Dr. Hoffsis: Thank you. I'd like to introduce Dr. Andrew Beaulieu. I had the distinction of being one of his professors at Ohio State a number of years ago, and so I'm pleased to see him rise to high position.

My reputation is on the line, Andy, so do a good job.

Dr. Beaulieu: Thank you. I'd like to also interrupt one slight detail. Do you feel we need the public address system, or? Maybe I'm right under the speaker. It seems really loud and harsh here. Or maybe we can turn it down a little bit.

Dr. Hoffsis: I was about to comment on that myself.

Dr. Beaulieu: These proceedings are a bit more formal than I'm used to. I have an aversion to podiums, or podia, or whatever this thing is. It looks kind of fakey to me. Maybe it's really a pseudo-podium....

?: Is that what you taught him in school?

[Laughter and comments]

Dr. Beaulieu: That was so bad, I'm reminded of Dr. Gable's scenario of the dart board, and to follow up on that, I might note that those folks that throw those darts don't always aim them at the dart board. I've had a few stuck in my anatomy from time to time.

The fact that Dr. Gable and I are speaking independently for preapproval activities and for marketing products in general does not mean that we make decisions on Rx-OTC status in a different way. We don't. We use the same criteria.

So I won't be saying anything about how we make Rx-OTC decisions differently from that which you've already heard.

I'll try to amplify some of the points made by Dr. Gable and offer a few others of my own. It's very important to reiterate that the regulation that provides for prescription status for veterinary drugs, that is, 201.105, should be viewed as an exception and not as a restriction.

502(f)(1) of the Act says that all products must bear adequate directions for use, and that's been interpreted to mean for lay use. Otherwise, it can't be marketed.

Now if it weren't for Section 201.105, it's quite clear that there are a large number of veterinary products which couldn't be marketed at all, because they cannot write adequate directions for lay use.

The courts have recognized this in our intepretation of Congress's intent in publishing 201.105, and have affirmed that interpretation in a recent appeals court decision.

Again, if adequate directions for safe and effective use by lay persons, they must be written, and the product must be marketed OTC. That was Congress's basic intent.

And so, in making the determination of whether

something should be Rx or OTC, it always comes back to can you write adequate directions for safe and effective use of the product by a lay person.

Now, it could be argued that every dog owner in this country has the right to try to diagnose congestive heart failure, and to subsequently digitalize their animals, and therefore, cardiac glycocides should be available at your local pet store.

Or for that matter, that dog owners should have general anesthetics available, so they can attempt surgery on their own animal.

But I've never heard such an argument made, and I don't expect to.

On the other hand, we might very well hear such an argument in terms of the rights and abilities of the food animal owner or producer.

Dogs and cats are largely perceived by the public to be like people in terms of disease diagnosis and drug administration. Food animals, however, are treated largely as property.

CVM's Rx-OTC determinations, which are based on the ability to write adequate directions for lay use of drugs, generally reflect these societal perceptions related to these two classes of drugs.

Most companion animal products are Rx, on the order of 80 percent of the companion animal products are prescription

products. And most food animal products are OTC.

If you consider dosage form of food animal products, it's on the order of 80 percent over-the-counter. If you throw in pre-mixes, that figure climbs to well over 90 percent.

While our society and its representatives in local, State and Federal regulatory agencies have traditionally recognized the relatively greater rights and abilities of food animal producers to obtain and use drugs on their animals, in terms of the potential affect this might have on the animals themselves, it seems to me that they have largely ignored the less philosophical and more practical issue of the effect this may have on their own health in terms of potential adulteration of their food supply.

Issues such as DES, chloramphenicol, the upcoming nitrofuran hearing, the antibiotic resistance issue, the premature thelarche issue -- although admittedly this has not been demonstrated to be food related at this point.

All of these issues may combine to sensitize the public and their representatives to the overall food safety issue, and this may result in a generally less permissive atmosphere.

If this occurs, a logical step for society to take would be to emulate the tried and true human health care system and place a greater proportion of drugs in the hands of trained health professionals, trusting them to protect its interests.

I suggest that in order for this to be recognized as

a viable approach, the veterinary profession must be perceived to be worthy of that trust.

Encouraging the veterinary profession to clearly recognize its responsibility to protect the public health, as well as the health of individual animal patients, is, of course, the heart of CVM's extra-label use policy. But that's another issue.

There are very good reasons why particular drugs are either Rx or OTC, largely because the people in CVM making these decisions really care about the impact that this decision has on animal and human health.

And more mundanely, because each such decision is subject to immediate contest via judicial or administrative proceedings.

While our reasons are valid, they are often complex, and to the uninitiated may appear arbitrary and capricious. As noted by the students yesterday, and others, for its part CVM needs to do a better job of explaining in general how it makes such decisions and why particular products are classified as they are.

It may have become obvious by this point that CVM takes these decisions very seriously, and we expect others to do likewise.

When they don't, we are empowered to take regulatory action. We may seize the involved product. We may enjoin the violators from further violation, or we may punish them for

past transgressions through prosecution and subsequent fines, and potentially imprisonment.

Usually, but not necessarily, violators are given a warning and a chance to halt their practices before further action is taken.

Our principal action to date, beyond a warning letter, has been injunction. Once an injunction is ordered by the court, that is, once the court orders a person to obey the law, any further violation of that law constitutes contempt of that court order.

Judges may react rather strongly to having their orders treated with contempt. Penalties in such cases are at the discretion of the court.

One of these injunction cases resulted in a District Court ruling that 201.105 was an invalid regulation. For a brief period of time, in one District in this country, there was no such thing as a prescription animal drug.

We appealed that decision, and the appeals court ruled in our favor.

In its decision, the court very clearly recognized that without this regulation, many vitally needed animal drugs wouldn't be available at all.

Dr. Gable has noted the factors affecting Rx-OTC status that are carefully considered when the product goes through the pre-clearance procedures in the CVM.

If you've already heard that many products currently

marketed never go through that process. We spoke of cardiac glycocides a while ago as examples of products that rather clearly require an Rx status. None of these products are formally approved by this agency.

Neither are they technically "old drugs," by the criteria established by the Supreme Court in 1973.

As with hundreds of other products, CVM has elected to exercise regulatory discretion and permit the products to be marketed at this time without formal approval, provided the products are adequately labeled to reflect the significant amount of published information regarding appropriate conditions of safe and effective use.

One of the conditions ... is that the products bear the prescription labeling. If a manufacturer of such a product elected not to accept the prescription status as a condition for marketing without approval, and marketed the product in the absence of the Rx legend, CVM would likely seize the product, not only because it was misbranded under 502(f)(1) of the Act, for failure to bear adequate directions for lay use, but also because it was adulterated under Section 501(a)(5) because it was not generally recognized to be safe and effective for lay use.

These two issues, of new drug status and prescription OTC status, are closely linked.

Thus, while CVM may elect to exercise regulatory discretion relative to such products when under the control of a licensed veterinarian, it may not be prepared to do so for

such products sold directly to lay persons.

However, in general, since most unapproved products, which CVM knowingly permits to be marketed are relatively innocuous, as a class, most of these products are OTC.

For example, topical products such as non-antibiotic ointments, udder ointments, teat dips, non-antibiotic wound dressings and poultices, hoof dressings, counter irritants, oral vitamin, mineral or electrolyte products, some parenteral vitamin or mineral products.

Taken together, these represent thousands of marketed products, none of which are approved....

In terms of market value, and this is a point I want to clear up about a comment I made yesterday, in term of market value, however, and actual volume of sales, while there are a lot of products involved in this class, the total dollar value and volume of distribution is probably far less than approved products, as a class.

Further on this issue, there are many products currently marketed without approval which do not fall in the classes above. That is, they are not deemed by CVM to be relatively innocuous.

And when we find out that such products are being marketed, we will take action to terminate that marketing, within the limits of our resources.

Many of these products are purported generic equivalents of currently approved products which have outlived

their patent protection.

Under the current system, there's no way for a user to know whether they are purchasing an approved product, or an illegally marketed copy of an approved product.

Our effort to permit identification of approved products on labeling may help to correct this situation, and it's that point that the students were trying to make yesterday, and I wholeheartedly concur with their recommendation, and we're proceeding along those lines.

There is one aspect of the Act, under 512(d), Conditions for Approving Products, which Dr. Gable alluded to, and that is the likelihood that directions will be followed in practice.

That is probably one of the toughest determinations for the Center to make, particularly in a pre-clearance mode. The product's never been marketed before, and therefore, there is no direct marketing experience. We have to make our best guestimate of whether the directions will be followed in practice.

In such cases, we probably err on the side of approving the product and closely monitoring it to make sure that our estimate is accurate.

There's one particular case which we're pursuing now involving the marketing of, the approval and marketing of oral chloramphenicol products, solutions intended for dogs, by stomach tube administration.

Based on all evidence currently available, it's quite clear that the overwhelming majority of that product is not going into dogs by stomach tube administration. It's going into cattle and swine.

And on that basis, we are proposing to withdraw those applications because the conditions of use established by the approval are not, in fact, being followed in practice.

To the best of my knowledge, it's the first time that CVM has ever proposed to withdraw an approval on that basis. We hope it will be the last time we have to do that.

I think for those comments, that's all I have to offer. Questions now, or later.

Dr. Hoffsis: We are a few minutes ahead of schedule. I think we could probably take a question or two right now.

I might ask one question. How large a part currently does the accuracy of a diagnosis play in the decision on a -- it was mentioned as one of the criteria by Dr. Gable -- and is that a major part of the decision?

Dr. Gable: One of the things, additionally, I said, is that we have to be consistent as well. It certainly is a part of it, and any one of these items cannot be divorced from the other

For instance,...I gave the example of the flukicide Clorsulon, there may be difficulty of definitively diagnosing. However, the state of the art shows, has shown us over the last few years, that there has been little or no attempt in endemic

areas to actually recover or identify organisms by fecal samples in that. Is it more important, we can't state that difficulty of diagnosis, if it's more important than others. It's certainly taken into consideration. I wouldn't want to rank it, I really can't rank it.

Dr. Crawford: In the B12 example, is that a useful one? I mean they have to be....

Dr. Gable: Andy's been struggling with that.

Dr. Beaulieu: In the unapproved product area, well, let's talk about... preparations as representative of the... Parenteral iron preparations,... over-the-counter, the reason there being that virtually all baby pigs are going to be administered the product with no diagnosis involved, given to the lay person, and can certainly write adequate directions to allow them to administer the product, with no diagnosis involved.

Vitamin E selenium products for white muscle disease, on the other hand, are Rx. Animals are not routinely treated prophylactically for that condition. You have to diagnose the condition and treat the condition. Those products are prescription on that basis.

A number of the unapproved products, vitamin B products particularly,... vitamin C, in fact, there is very little need for those preparations for the general indications of vitamin B deficiency in cattle or horses where it frequently appears on the labels of the products.

Technically, the conditions exist, but the average layperson is not in the position to diagnose those conditions, nor can you argue that the conditions are so prevalent that you ought to routinely give every animal a blast of vitamin B12.

On that basis, we believe those kinds of products should be prescription products. A diagnosis is necessary for safe and effective use of the products.

Even though they are themselves essentially innocuous, in terms of drug toxicity, they can't be used effectively except by a veterinarian, in our opinion.

Now that, that is probably the opinion that is most likely to be challenged in the near future by the industry, I would think.

A situation where we have a relatively innocuous product in terms of direct toxicity, but in which, for which we believe the Rx legend is appropriate.

Primarily, because of the need to diagnose the condition, and we may be arguing that in some form outside the agency.

Dr. Crawford: The countervailing argument is that the diagnosis may be made by a veterinarian, but that doesn't in and of itself mean that the veterinarian might not tell the animal owner to go to a hospital dispensary or drug store or whatever to get the drug.

Dr. Beaulieu: Yeah. One of the arguments you hear in general in terms of Rx-OTC marketing is, well, let's just

market the product OTC, but put a statement on there to the effect that, before you buy this product, get a veterinarian to determine whether you need it or not.

That gets to the issue of likelihood of directions for use being followed, and at this point, we are of the opinion that such directions are not likely to be followed in practice.

Another thing that has to be considered, and it's always a tough question is there are only two kinds of drugs, the prescription drug and the over-the-counter drug, and when you write prescriptions for lay use, do you write it -- there's a large span of abilities between producers as far as who do you write those directions to? Do you write it to the fellow who has a hard time reading a label? Or do you write it to someone who's been in the business and has an awful lot of expertise?

So that's another problem when you try to write it somewhere in between at the median of the ... variations you may have of that. That's not an easy thing, either. That's another thing that you have to consider in deciding who's are you really talking to when you write directions for lay use.

Dr. Hoffsis: Different levels of expertise among producers. I think that I, yesterday in my comments, brought up a question regarding vitamin E and selenium that you had mentioned, Andy, about that product being used essentially as a

management tool in sections of the country where deficiency is so widespread, it becomes a management practice of the same nature as iron injections with baby pigs.

And that's a little different situation than when the product can only be used after a diagnosis of white muscle disease has been established.

So, there's a kind of disparity in the thinking that develops over that kind of a question.

Dr. Beaulieu: On that point, if management practices change, if it becomes a general practice and an accepted practice by the profession, to generally treat all animals in a given area, then, under those circumstances, the prescription-OTC status of that product could very well change.

The status does change after products are approved, based on experience in the field themselves.

There's even a proposal, as Dr. Crawford mentioned, to make a large number of products Rx initially, with the intention of turning a lot of them into OTC products once you've gotten more experience with them.

I'm not commenting one way or the other on that, but in terms of how the Center deals with those issues, though, there are procedures established that any time that happens, everybody in the Center gets together, pre-clearance, post-clearance, everybody, and makes an assessment of that situation. We all work by the same criteria.

Dr. Hoffsis: Don.

Dr. Gable: I'd like to make a comment on the proposal of identifying CVM approved drugs. While that is very appealing to many of us, unless we have also entertained identification of the 80 percent of the products that Andy referred to that while not formally pre-cleared, for the most part have our sanction, unless we identify those as having such sanction, we add more confusion, I think, than benefit,if the objective is to identify products that are being marketed illegally.

Dr. Hoffsis: Any further comments at this point? If not, let's move on to the next topic, on the prescription-bulk drug issue, Mr. Gary Dykstra, who's Deputy Associate Director of Compliance with the Center.

Mr. Dykstra: First of all, good morning. I'd like to say that normally this time slot would be occupied by Dr. Bill Bixler, who would give you the status report, but we sent him off to the Eastern Mediterranean to check on the animal drug situation over there.

And we haven't heard from him since, so I don't know what's going on. I hope he's having a good time.

I'm the second team, but hopefully I still know a little bit about this subject. I'll try to pass that on to you today.

The illegal sale of animal drugs is a very difficult problem confronting the Center, and we think confronting the industry and veterinarians alike.

It's a multifaceted problem. The two major facets being the illegal distribution of bulk drugs, and the other facet being the illegal sale of animal drugs.

And what I'd like to do today is just tick off for you all the various initiatives that the Center has going right now, and there's quite a number of them, on both fronts, to try to get this problem under control, and generally give you a status report.

It's unfortunate, but I believe that you'll be hearing this status report for quite some time.

First of all, on the illegal distribution of bulk drugs, some time ago the Center issued an import alert concerning bulk drugs, because most of the bulk drugs are imported, the animal drug substances.

We hear reports and complaints all the time that these substances are widely available and anybody can get anything they want anytime.

That disturbs us a great deal. Because most of these substances, we felt that the best way to try to control that was to control it as its source, and that's the point of import.

So we issued these so-called import alert, which is a directive to all our district offices which serve as ports of entry to be on the lookout for these substances and assure that, first of all, the importation is bonafide, and second of all, to make sure that that bulk substance is going to an

aproved NADA holder.

Now, we've since found out that even with that assurance there may be problems, but I'll get into that a little bit later.

So, we have that import alert out there with our district offices, and by and large, we think they're doing a pretty good job of monitoring that situation, but it's fair to say that it's an overwhelming problem because of the nature of imports coming into this country.

First of all, we have to work with Customs, because they're the ones who have the initial contact with the goods. So we have to educate them as to what to look for. If they catch it, they let us know, and we follow up on it.

The other thing that we realized is back two or three years ago, most of these imported bulk animal drug substances were coming in through the Port of New York, not surprisingly.

So, we also figured that that being a primary source, we would get together with those people up there, our district office people, as well as the Customs people, and see if we couldn't work with them on a specialized program to control the situation.

And what we came up with was a pilot program that also involved the importers themselves. We talked to many of them and persuaded them, because we felt that it was in their business interests not to have FDA detaining every lot of imported animal drug coming in, to allow them to move that

substance to approved NADA holders, provided that they kept adequate and well-documented records that were available for inspection by Food and Drug, so we could assure ourselves that it was going to bonafide holders of NADAs.

So there was something in it for them and something in it for us.

That program has been pretty much a success, and we have not encountered a lot of problems in the Port of New York, whereas what has been happening, as you might guess, is because New York is so tight now, we suspect that importers are going through other ports.

So we're widening our horizons and branching out to other ports to see if that is indeed the case that they're moving to other ports.

With regard to strictly the illegal sale of prescription veterinary drugs, we have a wide-ranging program. First of all, we have instructions out to our district offices to be on the lookout for this kind of practice, and that has resulted, as Andy mentioned, in a lot of warnings to a lot of different groups and individuals not to engage in this kind of practice.

In addition to that, as you all know, we've been working with such groups as the AVMA to help us control this problem, and one of the most significant things that we did there is we encouraged them to develop a veterinarian-client-patient relationship definition, which is something that, I

think, has been widely accepted by practitioners, and is something that helps define again this situation of where a prescription veterinary drug may be lawfully sold and lawfully used.

The other thing that we've been doing -- and this is on the positive side of things -- is that we believe that most individuals out there are law-abiding citizens, and that if you give them enough information and enough education and the proper kinds of education, that they'll do what's right.

So a very, very important component of this overall program are the industry, education and information programs that we have ongoing.

In that regard, I think you've all seen, on one occasion or another, or heard, these speeches that have been given by Center managers around the country.

Over the last year, we have hit this topic in almost every speech that we give, and that's to give visibility to it, to sensitize people to it, and hopefully, to help keep the honest people honest.

The other thing that we've done in this education mode has been to work with various industry groups, such as the National Boards of Pharmacy and the Association of Food and Drug Officials and the Veterinary Distributors Association, any group that we think impacts on this problem, this program, we have met with and we will continue to meet with to search for ways in which we can work together to solve this difficulty.

Another thing that we did over the past year, and I think you're all familiar with that, was we went out with a suggested prescription guideline.

This at first didn't pan out as well as we had hoped. We had a difficult meeting on the subject last summer, where we thought that we could get some dialog going on the issue, but most people thought it was not a good idea at that time, that perhaps we were being a bit overbearing.

So what we've done in the interim is we have abandoned that effort by rescinding the proposed guidelines and have gone back to encouraging others to adopt those ideas.

So, while we believe we've lost the battle initially, it looks as though we may be winning the war on some fronts because many veterinary associations, as well as State officials, have picked up on our idea and are now actively pursuing it, which we think is a very positive thing.

On the issue of State involvement, this is another area that is of just absolute extreme importance because we think, like control of human Rx products, it's the States who really have the responsibility, and because the recognition of prescription veterinary drugs has not been very forceful or visible in the past, the States have not been very interested in stepping in to help either create standards of conduct, create licensing requirements, create a lot of other things and enforce them that we would like to see done.

So what we've been doing is try to sensitize the

States and State officials to this fact, and that's where the speeches to groups like the National Boards of Pharmacy and the Association of Food and Drug Officials have been extremely effective in getting their attention.

First of all, letting them know there's a problem and second of all, getting them to act, start taking some initiatives to get laws passed, to get resources to police this difficult problem.

That's a front that we will be working on very actively in the coming months.

The next thing I'd like to mention is an initiative that we took out in Iowa that was widely publicized. We think that was good. We think that perhaps some of the publicity was perhaps not well-founded, but it was an initiative that we took against veterinarians in the eastern part of the State of Iowa.

It was not a cold, calculated type of initiative. It was something that developed quite coincidentally, and really grew out of our investigations concerning chloramphenicol, and developed because some of our district people, in following up on chloramphenicol use and sales also noticed when they went into these veterinary clinics that they were also indiscriminately selling other prescription veterinar drugs.

In other words, the veterinarian wasn't even there. The clerk at the front desk would virtually sell you anything that you wanted. And the more they looked, the more they found.

After they got to a certain point, they said, "We think we have a problem in the State of Iowa." And those individuals came in and we had some high-level meetings here in the Center and talked it over and decided that maybe it is a total agribusiness type of problem, including the veterinarians, and that some actions needed to be taken.

It was decided that what we would do in Iowa is first of all, send some warning letters to these individuals who we had caught with the goods, if you will, and then follow that up, again, with our education effort.

In other words, give it some visibility first and warn these people, and then once the publicity gets and people are sufficiently concerned about it, then get together with all those people and tell them what we think of the situation and tell them what needs to be done to correct it.

So that is precisely what we did in Iowa, sent the warning letters to the individuals that we caught, not surprisingly, I think, they all, most of them, I think almost all of them came back and said, "Hey we're sorry. We got caught up in things. Competition is tough out here, so on and so forth. We won't do it any more."

That remains to be seen, but that was the tone of most of the letters that we got back. That was encouraging, by the way. We expected perhaps something on the order of an uproar, but that failed to materialize.

We followed that up, back in April, with what I think

was a very productive workshop out in Des Moines, Iowa -- well-attended by many veterinarians, both within the State of Iowa and surrounding States.

That session was well-publicized and I think we got a lot of mileage out of it. We have no more plans for those kinds of initiatives, but we are looking for ways to get the word that was passed to the people in Iowa out to other states because we really don't believe that Iowa is an isolated situation, so we're making efforts now to get that word and all that information that we passed on to those people around to other veterinarians throughout the country.

The last thing that I want to mention on this subject is that I ticked off a lot of things that we were doing, and we weren't quite sure whether we were having any effect at all, and perhaps we're not still quite sure, but we thought maybe it would be useful to have a third party come in and take a look at our overall program, look at all these different aspects of the program, things that we're doing, and see if that's the right direction to go.

So we asked our Associate Commissioner for Planning and Evaluation to send some of this staff in and critically evaluate this program to see if we were doing the right thing and going in the right direction.

And those people came in and it was a very enlightening, very refreshing type of experience for all of us. First of all, they agreed with us that we had a difficult

problem on our hands, and that it was difficult and very unique, and different from the control of human Rx...

And the important thing that came out of that evaluation is that first of all, they agreed with us that we still have a problem and that we need to continue with all of the things that we were doing. They agreed that they made sense and they weren't totally disjointed and for the most part we were going in the right direction, and that sensitivity and visibility was apparent and that hopefully sooner, rather than later, we would start to see some real benefits from this program.

Two important things that they pointed out to us, though, and I think we knew this, but it was helpful to have a third party point it out to us, was that the thing that we ought to be striving for -- two things -- first of all, we had real problems in the recognition of the Rx legend on veterinary drugs.

And I think you can understand that a little bit from Andy's and Don's presentations. A lot of the animal drugs out there are OTC. So that when you put the prescription legend on there, people aren't quite sure, really, what that means. Or at least that's what the appearance is.

So we have a recognition problem. The Center ought to be looking at that as a problem and do more things to solve that recognition problem.

The other thing that they recognized was that we

needed to continue with our efforts with State officials, and that what we really needed, because on the human side, things had worked so well, it was because we have a very good -- the word that they used is a "partnership" with the States on the human side.

The States accept everything that we do with human drugs, and they're willing to enforce that. That makes sense to them. We need to establish that kind of a partnership relationship on the animal drug side to get the States into the control of animal drugs, like strict licensing requirements and the policing of those kinds of requirements.

So I think I can safely say that I think we had that idea in mind, but it really wan't crystallized to that extent, and because of that, we are going to take a hard look at what we're doing, where our resources are, and perhaps refocus a little on those two primary goals over the next several months.

Doing something about the recognition problem, doing something about this partnership with the States.

That's all I have, Glen. If anybody has any questions, I'll be happy to try to answer it.

Dr. Hoffsis: Does the Committee have questions for Mr. Dykstra?

Dr. Lassiter: Gary, are you privileged to indicate which drugs are giving you problems on import now?

Mr. Dykstra: Sulfa drugs are one big group of drugs

that cause problems.

Dr. Lassiter: I remember in December something was said about DES. Are you still having a problem on DES?

Mr. Dykstra: It's not readily apparent. We're out there looking for it all the time. That's an easy one. We look for it. Customs is very sensitized to it, so we watch for it very carefully. Chloramphenicol is another one that we see on the import side.

Dr. Hoffsis: Bob.

Dr. Phemister: Yesterday afternoon, Dr. Guest referred to a letter from the Chairman of the AVMA Executive Board, Dr. Hopkins, who had presented a three-point recommendation to CVM. The third point had to do with bulk drugs, namely that the CVM publish a bulk-drug policy that would allow approval of drugs in bulk form for sale to veterinarians for use when a veterinarian-client-patient relationship exists.

I'd be interested in your comments on that.

Mr. Dykstra: As you know, that is a very sensitive issue. Some veterinarians want to and believe they are entitled to get bulk drugs to use in their practices.

The Center recognizes that and as a result of that we've had an ongoing effort, started initially by a task force in the Center, and ending with the drafting of a new policy statement, which we hope to publish soon in the Federal Register as a proposed change in policy, if you will.

Now, one thing that you have to recognize is because of the law, we can only go so far in that trying to help veterinarians in what they want to do.

We think that if they want more than that, then they have to get together and decide what that is, and then work towards changes in the law, really, that's what it's going to take.

But hopefully, in the not-too-distant future, you'll see the changes in policy that we're going to put out.

Dr. Schall: You were talking about OTC and prescriptions, and prescription says on the label. You see a lot of them that says, the label says "Restricted." What would that mean?

?: Gary, could you repeat his question. I don't think everybody could hear.

Mr. Dykstra: OK, he said that on the prescription veterinary drugs, you have the standard caution legend, which is prescribed by regulation. But you also see other terminology, such as "Restricted" or "Sold only to veterinarians" and things like this.

All that this reflects is the sales policy of the manufacturers. That's something that we don't control. We don't get into that aspect of marketing. That's up to them.

Dr. Crawford: Gary, if that were felt to be a deceptive practice, it would be our position that that's something for the Federal Trade Commission to deal with?

Mr. Dykstra: Yeah, we could discuss it with FTC, or we could take it directly to the manufacturer ourselves and discuss it.

Dr. Beaulieu: There are one or more States which require certain statements to appear on labels, "Hazardous to livestock...," statements on that order. Provided they're not misleading in any way, we go along with the states and approve the products with those statements on their labels. We'll see statements like that.

The one that Mr. Dykstra was talking about, "Sales... to veterinarians only," which is sometimes seen in the absence of a prescription legend is purely a sales policy of the firm.

That's an over-the-counter product which they elect to sell only to practicing veterinarians.

Dr. Hoffsis: I made a comment about that yesterday, and as a personal opinion, I think that kind of legend does significantly lead to the confusion among producers.

And not only that, but among professionals as well, because it would imply to someone who doesn't know the intricacies of the regulations, that when it says it's sold only to a graduate veterinarian that that means it's sold only to a graduate veterinarian, and yet, if a product like that is sold over-the-counter, then maybe the other legend, which is the prescription legend, takes on a little less reverence.

And I think that significantly contributes to the confusion. There's a general disregard for all of those

legends.

Mr. Dykstra: That's part of that recognition problem that I was talking about, and something that we will address one way or another. Anything else?

Dr. Hoffsis: I had a question about the compliance efforts and the direction that they're taking.

The indications I have is that there is a significant and rather massive effort that is targeted at practicing veterinarians in their practices of selling prescription drugs over-the-counter.

And I wonder how you perceive that same problem with lay distribution centers, and do you currently feel that that is still a major problem?

Mr. Dykstra: OK. In the past, our perception was that the problem lay with the distributors. As a consequence of that, most of our effort and resource was put into looking at this segment of the industry, and all the actions that we took were against this segment of the industry.

This segment of the industry has now become either more compliant or more clever in how they distribute drugs and sell drugs.

That's not to say that we still don't have a very intensive effort going against that segment of the industry.

What's happened again, as I said, as a result of our chloramphenicol efforts is we started to get into the veterinary clinics, looking first for chloramphenicol, but

later finding that they were selling drugs illegally in some cases.

As a result of the Iowa effort, some of our other district offices -- even though we have no directed program in this regard -- have picked up on that idea and are looking for it, quite frankly.

The only thing that we've told them is that you ought to do that in a very professional way, first of all. And second of all, if you're contemplating any kind of major effort, let us know about it, so that we can talk about it and decide the proper course of action.

But as I said in my remarks, we believe that the veterinarian is somewhat part of the problem, needs the education and information that we're putting out there, and given that education and information, will stop the practice.

So right now they are getting some visibility. We don't expect that that's going to continue for any length of time.

Dr. Crawford: I think a couple of examples support the contention that many of the things that we deal with are resulting from local custom.

In Iowa, as has been mentioned, it had become usual for veterinary hospitals to have display gondolas which offered prescription drugs as well as over-the-counter drugs for essentially lay sale.

And I'm not sure that occurs to that extent in every

State. I would suspect that states may differ.

In Puerto Rico, you didn't mention the same kind of program, but essentially what we're doing in Puerto Rico is the same thing that we were led into in Iowa.

And down there, they have some local customs and apparently, some legal justification for allowing pharmacists to sell prescription veterinary drugs and prescription human drugs over the counter.

It's unresolved whether or not a veterinarian or a physician may do the same sort of thing. Our several-month campaign in Puerto Rico, in concert with the Department of Health there, will probably lead to some changes in their Commonwealth regulations, laws and maybe even customs.

This is, these two examples are the greatest supporting evidence for trying to somehow or another devolve these responsibilities to the States, because the States either need to clamp down very stringently or they need to figure out some way to license people that distribute drugs and give them some kind of leeway and work out workable agreements with the Center for Veterinary Medicine where they can serve as a contract team for enforcement of these sorts of thing, or something like that, because the demand for veterinary drugs in the Texas panhandle are probably greatly different from what they are in Puerto Rico, and yet they are regulated and legislated the same way.

And that has been one of the problems that Gary

Dykstra and his staff and the field people have run into, because, you know, when you get into the West, or you get into the poultry area of the Deep South, or you get into Puerto Rico or Alaska or Hawaii, the Samoan Islands, things are just different.

I was visited by a veterinarian, a Western veterinary conference in Las Vegas in February, and he's from Kodiak Island. He's the only veterinarian on Kodiak Island, and he's not a practicing veterinarian. So they've got a problem on Kodiak Island, that became my problem that afternoon.

So I think some kind of devolution to the States and some sort of long-range strategy for energizing State boards of pharmacy and State boards of veterinary medicine will be the eventual solution to much of what you've said.

About those mail-order houses, a lot of them now, if you look, have statements saying they will sell prescription drugs only if they have a prescription on file, etc., etc., etc.

There's been a great change in that industry in two years. The major suppliers generally have, I think you'll agree, become more compliant. You said, "or more clever." It may be the same thing, I think you'll also agree.

We had to be sure that it is more compliance than it is cleverness and we are doing that now.

But there has been a change there, and there's been a change in the way veterinary drugs, I think, are dispensed in

general, but we're not there yet, you'd agree.

Mr. Dykstra: And there seems to be a general perception, particularly amongst veterinarians, that we have singled them out for some kind of special attention, and that just isn't true.

We're investigating just as many dealers and distributors, if not more, that we are, certainly, veterinarians.

Dr. Hoffsis: John.

Mr. Megown: I'm from Iowa, Eastern Iowa, as you know, and I've been watching it from a lot of different directions. It's not as rosy and pleasant as you think, nor has it died down.

In fact, I think the Eastern Iowa veterinary medical thing has, they've got a cause that they've united behind, and even the vets that weren't involved are defending their brothers against the big brother in Washington.

And they have some beautiful stories...

?: Can you speak up a little bit?

Mr. Megown: OK. They have some beautiful stories, for example, I know of the man that's in charge of that that one of the ways this happened to happen, accidentally, was the vet went down to the coffee shop with a farmer and his wife and had coffee, and while the vet and the farmer had coffee, she went back and bought the material, and that's how come these things happen, and so forth.

So, they've been able to organize pretty well and to keep it alive, and you mentioned the chloramphenicol investigation, they've kind of turned that one around in recent weeks, and now, they say what brought this about was the low-level antibiotic feeding and so forth, and this salmonella outbreak and so forth, and they're taking the brunt of the attack on this.

So, I just wanted to get that into the record, that if you accomplish scaring them to death, they're still operating, a lot of them, and they have now learned how to handle public relations better than they used to.

Dr. Crawford: Yeah, I would also say that in the case of Iowa, we had probably the best cooperation we've had by State authorities throughout the whole thing.

So, the meeting that Gary mentioned was actually sponsored by the State veterinary medical association and funded, to some extent, by the office of the State veterinarian and the State regulatory authorities.

So it is, I think it's big brother, not only in Washington, but maybe in Des Moines.

Dr. Lassiter: Gary, you spoke about these State-controlled ..., in your comments that it's something less than optimum, had better...

Mr. Dykstra: Yeah, it had...

Dr. Lassiter: Are we dealing with a State rights issue, or dealing with a lack of resources at the State level?

Mr. Dykstra: OK, we're dealing not with States' rights. We're dealing with a lack of State legislation, first of all, and second of all, resources.

What we're trying to do, we've got two initiatives going right now that are kind of interesting, to help that out, in addition to just putting a lot of information out to the states, and failed to mention in my remarks, but they are significant.

First of all, on the legislation side of things, we are encouraging States to look at their current legislation to see how it deals with animal drugs, and if it's weak, do things to strengthen it.

In that regard, what we're going to do to try to help them is develop a model State code, which we've done in a number of areas, particularly on the food side, that States generally adopt these things, either in whole or in part.

Dr. Lassiter: Similar to milk?

Mr. Dykstra: Right, right. And we've got that initiative pretty much under way now, and hopefully, in the next several months, we'll have a model that we can pass around.

The other thing that we're doing on the resource side is we thought, you know, we have a few contract dollars, why don't we go out to some of the states that do have some laws, but don't have the resources, and give them a few dollars and let them see if they can enforce their law. Hire a person or

something like that to go out and do some police work.

Dr. Crawford: Yeah. That all focuses on the unbelievable incongruity that from time to time, State regulatory authorities call us or give press releases and ask why we aren't doing more with this horrible problem, when it's really more their problems than it is FDA's. Ours is sort of a last resort effort.

Dr. Jenkins: Can I ask Gary, who do you contact in the State? The State health service, which then filters down somehow to the veterinary department?

Mr. Dykstra: Well, as you can guess, every State is a little bit different. Some States, it's the health department. Some States, it's the agriculture department. Some States, it's both, which causes difficulty.

Sometimes the State veterinarian works for one department as opposed to the other. Sometimes they're involved, sometimes they aren't. It's difficult.

And we almost have to work with it on a State-by-State basis, which really makes it a difficult task.

Dr. Jenkins: Because even the upgrading of their laws becomes difficult. That has to come from the State congress in one state or another.

Mr. Dykstra: Yes.

Dr. Jenkins: So they need sponsors. It's not an easy chore.

Mr. Dykstra: But it's amazing. Over the past year,

we've seen several States pick up on this issue, and they are taking steps to look at their laws and enhance them.

Mr. Megown: Lester, that's something I wanted to ask you. Doesn't Iowa, don't they have a recent law that does this?

Dr. Crawford: Yes, Iowa just changed its law, and joined an increasing number of States -- Gerry, help me with this -- Tennessee is doing something.

?: California.

Dr. Crawford: California, and Oregon also.

Mr. Dykstra: Wisconsin.

Dr. Crawford: Illinois, Wisconsin. See because they are understandably concerned about the mail-order houses operating within their boundaries or shipping in catalogs from outside.

They're also understandably concerned about so-called drug peddlers, etc. They can deal with them a whole lot better than we can.

In most cases, it involves them enforcing laws that they already have. In some case, a few cases, they probably need some more laws, or at least to go through the exercise of re-examining the law that they do have.

So we just, you know, really need to raise their energy level. I think that's essentially what we do.

Mr. Dykstra: An interesting aside -- I got a call from the person associated with the State legislature in

Connecticut, and one of the options that they were considering is controlling animal drugs just the way they control human drugs. You can only get them through a pharmacist.

And we had a long discussion about that. I said that they may have some real problems with that, but that certainly is the far side of the spectrum.

Dr. Jenkins: The other question I want to ask, do you routinely keep the State veterinary associations informed on policies made, or you're seeking input? Is it standard practice to approach the State veterinary associations for comment and input?

Mr. Dykstra: OK, generally we work through the national association, the AVMA, but we are in increasing numbers getting contacts from State veterinary associations, as well as the specialty associations -- Swine Practitioners, Bovine Practitioners, and those groups.

Dr. Crawford: When we have a situation like Iowa and Puerto Rico, we always deal with the veterinary association. The Puerto Rican all-day meeting, again, was co-sponsored by the veterinary medical association.

And if we, for one reason or another, were unable to get their cooperation, then that would probably mean there wasn't a problem. So it is a good suggestion that we always deal with them.

Dr. Jenkins: Because, again, the States do, such a diversity between States that dealing with the AVMA is

certainly excellent and correct, but they might represent every State equally.

Dr. Crawford: The other thing we've found to do with State VMAs is that they are helpful in creating grass-roots support, because they're usually the most concerned and if something needs to be done in the Statehouse, they're a lot more effective in dealing with it than we are -- to wit the Iowa experience.

Audience: The whole leading background is this concept of the bulk drug...

?: What is your name, please?

Dr. Woulfe: Maurice Woulfe. The whole concept of this bulk drug thing, I think, has not been resolved in the legal aspect. I've got some real problems with this business of also the drug company being required to come up with stability and ... considerably. You are now proposing to import various drug from abroad, give them to a veterinarian, who will put them together under whatever circumstance...

Dr. Crawford: Let me interrupt you...

Dr.Woulfe: Hold on.

Dr. Crawford: Well, I'm sorry, but that's pending regulation that we can't comment on. You're saying what we're proposing to do. We can't say what we're proposing to do.

When and if such a regulation publishes, you may make comment legally, but it's extra-legally at this point.

Dr.Woulfe: So long as we have no discriminatory

treatment under law, I'm quite happy about that.

Dr. Crawford: I appreciate that, and of course, knowing me as well as you do, you know that would never be the case. But what you can do is you can say, just don't talk about the regulation. If you'd like to make a statement, say with respect to bulk drugs, the position of your company is as follows. Read that in the record, shoot.

Dr.Woulfe: What we would like to say then is that we trust that the sponsoring drug company would be treated in the same manner as a manufacturer as this new veterinarian, who's also a manufacturer, in that he will in all probability extend the sale of his drugs beyond his client-veterinarian relationship.

Dr. Hoffsis: Dr. Bechtel.

Dr. Bechtel: I'm David Bechtel, and I'm from the Texas Panhandle, and I appreciate Dr. Crawford's saying that we do think different than in the east, because we do, and I think this is one of the things I'd like to bring up.

You've been talking about the negatives all morning, and there are a lot of States and a lot of areas of a State that do a lot of things right. I think you should promote these things, just go out and stress the positive and quit talking about the negative, it would sure make a big difference.

I would also like to comment about the pharmacist ... doesn't always why it happens. This is one of the reasons in

the Texas Panhandle, a lot of mobile distributor companies got started, because there were a lot of local pharmacists in the rural areas that tried to distribute the veterinary drugs, and they themselves were making diagnosis, this type of thing, selling prescription drugs when they shouldn't be.

So I don't thing you should really put a white hat on that pharmacist, either. You should go to the veterinarian who is the animal livestock producing pharmacist, and make him aware of how other people are doing it that are doing a good program, and approach it that way.

Mr. Dykstra: I hope I gave that impression in my remarks in that certainly one of the most important aspects of this program is the information portion of it, and the attempt there is to help the honest people stay honest.

We think that that by and large is the greatest proportion of the people out there. That's really what we want to do. If we can make that group larger and larger and larger, eventually we won't have a problem.

Another thing is, we talk about this as the illegal sale and distribution of veterinary drugs. It's also the increasing probability that every veterinary drug sale will be a legal sale, if you want to put a positive tone to it.

Dr. Hoffsis: Any other comments from the Committee? I have one question I'd like to address, maybe to Dr. Gable or Dr. Beaulieu.

We heard yesterday, I think from the students

actually, alluding to the fact of a some sort of compendium that would list all of the approved and designated prescription or over-the-counter drugs, and I know there have been some attempts at this from various publishers, but is there an official listing or compendium that might help practitioners and distributors and whoever, that would have an interest in this, to distinguish between these different classes of drugs? Is it available today?

Mr. Dykstra: I can comment on that. I think maybe Dr. Crawford could, too. That initiative -- we recogize that as something that's very definitely needed -- and that initiative has a very high priority in the Center.

We have various forms of that kind of a listing, but nothing as comprehensive as you have described. We are working on that and hopefully within the not-too-distant future, we will have such a compendium of drugs which will be available to veterinarians and others alike.

Dr. Hoffsis: Until that time, then, our best practitioners' or producers' best chance of determining that is to look at the label, and we can't tell if it's approved or unapproved by looking at the label.

We can tell prescription or non-prescription.

Mr. Dykstra: OK, you want to say some words about the labeling initiative, Andy?

Dr. Beaulieu: More on that score, back in 1938, Congress determined that human drugs should not be permitted to

identify their approval status. That is specifically forbidden today, under 301(L), I think.

Devices -- when the device legislation was passed, they also..., can't say that about a human device, either.

There is no such restriction against identifying approved veterinary products on the label or advertising... There never has been.

There is nothing right now to prevent veterinary drug manufacturers so stating. We've had a compliance policy guide which indicates that if they want to do that in advertising, they ought to do it a certain way, so that it's not misleading...

The initiative we're talking about now is simply to make it generally known that that option exists, and the manufacturers elect to place that information voluntarily on their labels, we'd like to give them some guidance as to how to go about doing that to achieve uniformity.

There will be, that initiative will be made publicly available in the near future in terms of -- essentially those terms are if you want to do it, this is how we'd like you to do it.

There will not be a requirement. In order to require manufacturers to do that, we clearly have to publish proposal regulations and public final regulations. We're not proposing to make it mandatory at this time.

That will allow practitioners access to information

directly on the label as to whether that particular product is the subject of an approved new animal drug application or not.

There may be a cost differential between a product that bears that labeling and one that doesn't, and the practitioner will have to decide for himself whether it's worth it to buy the approved product....

Dr. Crawford: The underlying trouble with all of this is that it was the clear intention of Congress in '38 and reaffirmed in '76 that products not be identified as being FDA approved.

There's a loophole that allows us to do this with veterinary drugs as they're not specifically mentioned in, but it's a loophole we haven't chosen to close because we wanted it it wasn't just an omission. That's the whole deal right there.

Dr. Hoffsis: Further comments? Anyone else from the audience? We are running a little bit ahead of schedule, and my inclination with no dissension from the Committee is to take a slightly longer break than scheduled and to reconvene at the next topic time listed on the schedule at 10:45. So we'll have about a half-hour break.

[Break]

Dr. Hoffsis: We have a discussion on low-level antibiotics, and to begin that discussion will be Dr. Lester Crawford, and Mr. Phil Frappaolo will discuss the status and the issue from the vantage point of the FDA.

Dr. Crawford.

Dr. Crawford: Thank you. OK, this morning Phil Frappaolo is going to discuss the situation with the low-level antibiotics in terms of what has happened to them since 1984. He will, therefore, be discussing that which most of you are interested in.

And I proposed at this point to introduce the subject by giving a little bit of background, in terms of how we got to 1984.

The Center for Veterinary Medicine first began looking at this issue in the early 1970s, and at that point a task force, which included some of the people that are here today, looked at the issue subsequent to some initiatives that were taken in Great Britain to limit the use of these two antibiotics, and made a recommendation which essentially was that no new human use antibiotics be added to animal feed.

That was codified in, among other things, a regulation called 558.15. Subsequent to the publication of that, there were some antibiotics that were obviously human use antibiotics, especially including penicillin and tetracycline, but also even some antibacterials, like sulfaphenoxylin, that were looked at by a task force, which was a subcommitee of the National Food and Drug Advisory Committee.

In 1976, they made a report to the Commissioner of the Food and Drug Administration following looking at essentially the antibiotics that were already in animal feed that had human use as of 1973.

That resulted in the 1977 orders from Food and Drug, which proposed restricting tetracycline usage and eliminating penicillin use in animal feed.

After reviewing that to some extent, the Food and Drug Administration decided that this was an issue that required an administrative hearing.

And rather than take summary judgment on these two antibiotics, the Commissioner and me announced in the summer of 1978 that we would eventually hold administrative hearings on the subject of limiting these two antibiotics.

After that, Congress intervened and suggested that we contract with the National Academy of Sciences for a thorough review of the subject, which was done, and in the course of actually two looks by the National Academy, it was recommended that we from certain research projects in order to get to the bottom of the issue.

Those were done and were completed in 1984, and at that time then the issue heated up again and we have now made testimony before the House of Representatives in December and also before the House and Senate budget committees in March and early April, relative to this issue.

Also, we have had, as you know, an imminent hazard petition from the Natural Resources Defense Council, and all of this leads up to what Phil has to discuss relative to 1984 and beyond, which is your topic, Mr. Frappaolo.

Mr. Frappaolo: Thank you. Literally, figuratively,

I'm the man in the hot seat, I guess. Les tells me if I don't get this thing figured out one way or the other that I'll be the lighthouse keeper on Kodiak Island.

And so, one way or the other, we're going to try to get something accomplished. Some of the ground that I will go over Les has just alluded to. I'm not sure how much background you all have in antibiotics in animal feeds.

Obviously it's been an issue that's been before us since the mid-1960s, with the advent of the Swann Committee Report in '69, of course. The agency then went in, as Les said, to its own task force type mode. In 1972, we did have a group work that issued.

So let me just go into these things and then we can discuss the '84 situation and what's happened in the last several months, and get into some of the current studies that we're looking at.

The Center for Veterinary Medicine has been concerned for some time about the possible health hazards posed by the use of antibiotics in animal feed.

In particular, the Center is concerned about the long-term subtherapeutic uses of antibiotics in animal feeds.

These are used for improving feed efficiency, rate of weight gain, and for disease prevention, plus these uses promote the development of drug-resistant bacteria in animals and the routes for the movement of these resistant bacteria to man are available.

The Center believes that drug resistance and the bacteria associated with food animals can affect the portion of drug-resistant bacteria that cause human disease. Therefore, the potential exists for compromise of drug therapy in animals and in humans.

In late 1977, as Dr. Crawford just said, the Bureau for Veterinary Medicine, which is now the Center for Veterinary Medicine, published proposals in the Federal Register to restrict the addition of low levels of certain antibiotic in animal feed.

These drugs are penicillin and two tetracycline drugs, oxytetracycline and chlortetracycline, and combination products containing these particular antibiotics.

Penicillin and the tetracyclines were chosen because of their importance in the treatment of human disease.

The Center's concern that the continued unrestricted subtherapeutic use of these antibiotics presents risks to human and animal health is based upon consideration of a number of factors.

First, long-term low-level feeding of penicillin and the tetracyclines promotes by natural selection from the pool of normal intestinal flora those enteric bacteria that contain R plasmids.

Now R plasmids, also known as R factors, are extra-chromosomal genetic material which confer antibiotic resistance to host bacteria.

These plasmids can be transferred between various kinds of bacteria through cell-to-cell contact or conjugation. Simultaneous resistance to several unrelated antibiotics is commonly carried on a single plasmid, and therefore, is simultaneously transferred from one bacterium to another.

Second, E. coli strains bearing R plasmids can be transferred from animal to man. Under the proper circumstances, organisms of animal origin can colonize in the human gut because the transfer of that can occur within a short period of time, and it is only necessary for one transfer to occur.

However, colonization is not considered necessary for transfer of drug resistance to strains that inhabit the human gut.

Third, factors associated with pathogenicity of E. coli have been shown to occur on the same plasmid as drug resistance and drug resistance in pathogenic factors have been co-transferred from one bacterium to another.

And last, R plasmids can be transferred from normally non-pathogenic E. coli to certain pathogenic strains of bacteria, with which they come into contact in man and in animals.

Now, since R plasmids carry drug resistance, this transfer can result in the creation of pathogenic strains of bacteria which are resistant to antibiotic therapy.

Now that's the crux of the FDA case as was presented

in 1977 in those notices of opportunity to the hearing.

Now, continued unrestricted subtherapeutic use of antibiotics in animal feed increases the pool of drug resistant bacteria in our environment. Moreover, the prospect of pathogens becoming drug resistant is a real threat to human health.

This risk is demonstrated by recent emergence of human diseases.

In short, the evidence suggests that enteric microorganisms associated with food animals and man are R plasmids and human pathogens form a linked econsystem in which action at any one point can affect every other.

But the vulnerability of microorganisms to antibiotics is reduced by antibiotics for non-medical purposes in animals, the effectiveness of medical treatment will be diminished in man.

Potential risks to animal health also exists, and while the linkage to human health is indirect, animal agriculture faces the risk directly.

Development of resistant strains, which is enhanced by subtherapeutic drug use, reduces the efficacy of those same drugs for the treatment of a number of diseases.

Now, as Les said, since the early 1950s, the practice of using low-levels of antibiotics in animal feeds has steadily increased, particularly in feeding of beef cattle, poultry, and swine.

Soon after the feeding of low levels of antibiotics became popular, scientists in the United States and other countries began studying the effects of and the practice very early on, and they expressed concern about the continuous long-term use of low levels of antibiotics.

Between 1970 and 1977, FDA had directed several groups to review the use of antibiotics in animal feeds. As a result of those studies and these groups and the groups' recommendations, Commissioner Don Kennedy in 1977 said that the Center should proceed with proposals to withdraw the subtherapeutic uses of penicillin and tetracycline from animal feeds, both alone and in combination.

Low-level use of the tetracyclines was to be eliminated except where no substitutes were available, and that's with respect to antiplasmosis and shipping fever complex.

In 1977, FDA stated that the statutory procedures for revoking present approvals by publishing in Federal Register detailed proposals to withdraw subtherapeutic uses of penicillin and the tetracyclines from animal feeds, with corresponding notices of opportunity for hearing.

Also at that time, a third document was published in early 1978, I believe it was January, which was the controls document, upon which we held several hearings out in the Midwest and other areas of the country, which proposed to put the remaining uses under a veterinary prescription.

In 1978, as Lester indicated, the Congress allocated money for a study of the entire antibiotics in animal feeds issue to be conducted by the National Academy of Sciences.

The House Appropriations Committee, in its report on FDA appropriations, also stated that FDA should hold in abeyance any implementation of a proposed withdrawal action, pending completion of the study.

In addition to the NAS report, other Congressionally mandated studies were completed, including a 1978 report by the United States Department of Agriculture and a 1979 study by the Office of Technology Assessment.

These reports essentially supported the agency's scientific concerns.

On March 18, 1980, the NAS released its report, "The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds," prepared by its committee to study the human health effects of subtherapeutic antibiotic use in animal feeds.

The NAS committee concluded that existing data had neither proven nor disproven the postulated hazards to human health from subtherapeutic antimicrobial use in animal feeds. The NAS committee also stated that the lack of data linking human illness with the subtherapeutic use of antimicrobials must not be equated with proof that hazards do not exist.

The NAS committee went on further and stated that the research necessary to establish and measure definitive risk has

not been conducted, however, in the committee's opinion, it might not be possible to conduct a single, comprehensive epidemiological study of the effects of human health resulting solely from the subtherapeutic use of antimicrobials in animal feeds.

The NAS committee suggested several less comprehensive, but more feasible studies that had the potential to clarify certain points, although not all issues will be settled.

It was hoped that the suggested studies would better define the links in the chain of events that is believed to exist from feeding of subtherapeutic levels of antibiotics in animals to the development of drug resistant disease in humans.

Now, on the appropriations, just about the time that the NAS report was issued, the appropriations report for FY81 provided money in FDA's budget for definitive epidemiological study of the antibiotics in animal feeds issue.

Again the committee stated that we should hold in abeyance any and all implementation of the proposed withdrawal, pending completion of the studies and re-evaluation of FDA's concerns.

In response to the Congressional mandate to generate additional data, FDA awarded a contract to the Seattle-King County Department of Public Health to conduct an epidemiological study of salmonella and campylobacter in commercial meat products in the community, and their

association with human disease.

In August of this year, of 1984, the Center received the final study report, which has been accepted as having met contractual obligations to this point. Also, we've been reviewing it these last several months.

This study, along with other studies conducted under FDA contract, is still undergoing scientific review within the Center by the Center staff.

FDA is also conducting a worldwide literature search to review all available research and other information with respect to this particular issue.

Now, the 1977 proposed withdrawals were criticized on the grounds that there was not adequate epidemiological evidence demonstrating that drug resistant bacteria of animal origin are commonly transmitted to humans and cause serious human disease.

In addition, there were no specific instances in which the feeding of subtherapeutic antibiotics to animals was associated with subsequent development of disease in humans.

So that brings us up to about 1984 and the events that have occurred in the last several months with respect to several studies, and let be just briefly review them for you.

First was the O'Brien study, which was condcted at Harvard Medical School, at the Brighamton Women's Hospital. This study, which was published in 1982 in the New England Journal of Medicine, the researchers were able, using a new

biochemical technique to trace genetic components, R plasmids, of various strains of Salmonella bacteria. The researchers found that R plasmids in some bacteria in man and food animals are genetically similar or virtually identical.

They concluded that this similarity is evidenced that antibiotic resistance bacteria may be transmitted between food animals and man on a widespread basis.

Seattle-King County Study -- this was designed to determine the relationship between the occurrence of human diarrheal illness caused by Salmonella and Campylobacter organisms and the occurrence of these bacteria in foods of animal origin.

Thus Salmonella and Campylobacter would serve as models to estimate the flow of bacteria from animals to man through the food chain.

The study used a dual surveillance approach, one which monitored cases of human illness and the other involving the sampling of meat for contamination.

For human case surveillance, all cases of Salmonella and Campylobacter enteritis diagnosed in enrollees at a Group Health Cooperative of Puget Sound, a 320,000-member health maintenance organization, were investigated over an 18-month period.

Control subjects for Campylobacter cases were also investigated.

Food surveillance was integrated into the Health

Department's meat inspection program, and thus provided access to all retail purveyors of meat products in King County, Washington.

Added to the retail meat surveillance system was the specification for culturing poultry products at a large independent poultry processor in Seattle.

In order to evaluate relationships among individual Campylobacter and Salmonella isolates, antibiotic susceptibility testing was conducted, along with serotyping and several types of plasmid analysis.

Now the contractor reported that a significant portion of poultry samples collected at retail outlets and from the poultry processing plant were contaminated with Campylobacter.

Other meats had a much lower order of Campylobacter and Salmonella contamination rate. The complemented the results of the investigation of case and control subjects, in that the contractor estimated that nearly one-half of all of the Campylobacter cases was attributed to exposure to poultry.

The contractor concluded that enteritis due to Campylobacter is more common than due to Salmonella, and that Campylobacter, including resistant strains, appears to flow from chickens to man via contact with poultry products.

Now the next two studies are the most controversial studies, and those were the ones done by the CDC, the Scott Holmberg Study, in which Dr. Scott Holmberg and others at

the Centers for Disease Control report on a retrospective analysis of outbreaks of human Salmonella infections in the United States.

Fifty-two outbreaks of antibiotic resistant Salmonella infections over a 13-year period were examined. The researchers stated that the fatality rate was much higher for persons with antibiotic resistant infections than for persons with antibiotic sensitive infections.

It may be important to note that this particular conclusion was the one that was most criticized at the hearing held on January 25, 1985.

They also concluded that the food animals were a major source of antibiotic resistant and antibiotic sensitive Salmonella strains.

Apparently, antibiotic resistant bacteria frequently originate from food animals and can cause serious infections in man.

Another report by Dr. Holmberg and others at CDC appeared in the September 6th issue of the New England Journal of Medicine. This study received widespread attention in 1984 and certainly through '85.

Eighteen persons in four states had contracted Salmonella infections with multiple antibiotic resistance, and the researchers concluded that the bacteria originated from a beef herd in South Dakota that had received subtherapeutic antibiotics.

The researchers concluded that antibiotic resistant strains of bacteria of animal origin can cause serious human illness.

Now the Center is currently continuing to review these data, in addition to other information in the literature that we're starting to collect since 1977.

On November 20th of 1984, Secretary Heckler received from the Natural Resources Defense Council a petition to declare the subtherapeutic uses of penicillin and the tetracyclines in animal feeds an imminent hazard to the public health.

The NRDC argued that, on the basis of three recently published scientific studies, the O'Brien and the two Holmberg studies discussed earlier, FDA is likely and eventually to withdraw approval of the subtherapeutic uses of penicillin and tetracyclines in animal feeds.

The NRDC argued, based on these studies, that these uses meeting the criteria for an imminent health hazard under the law.

So before making any recommendations to the Secretary, the agency must evaluate all available information, not just the three studies cited, but other available information.

And to assist in this process, the agency held a public hearing on January 15th, 1985. It was a legislative-type hearing 21CFR, Part 15, in which interested

persons were invited to present their views.

Notice was published in Federal Register of December 21st, 1984.

Now the criteria used to evaluate the human health hazard petition are as follows:

First, that the likelihood that FDA will eventually withdraw approval. Second, the severity of harm any withdrawal withdrawal of approval.

Third, the likelihood of our impending withdrawal of approval. Fourth, the risk to treated animals from suspending marketing of the drug products, and certainly other approaches to protect the public health.

The NRDC petition was evaluated by the agency, and a report was generated and forwarded to Dr. Crawford two weeks ago.

That report has since been forwarded to the Commissioner.

Now, as you can understand since the recommendations in that report are of such a nature that only the Secretary can make the announcement with respect to that petition. We're not at liberty at this point to discuss the recommendations of the petition.

It must be understood that the human health hazard petition, under the law, is a non-delegatable authority. Only the Secretary of Health and Human Services can be the one to announce, one way or the other, whether she agrees with the

recommendations that the agency has forwarded. And that's probably one of the best-kept secrets of the agency, I think, because not even the Associate Commissioners were privy to the document itself. There were very few copies of it that were forwarded.

So, that's where I can leave you at this point. I'd welcome any questions, and try to answer any of the things we possibly can within the context of this hearing.

Dr. Hoffsis: Thank you, Mr. Frappaolo. I'd like to limit any questions and only a few then to the Committee then at this point.

Anyone have a question, an additional piece of information...?

Dr. Lassiter: ...Will you repeat that last few statements you made about the Secretary.

Mr. Frappaolo: A human health hazard petition is a non-delegatable authority. In other words, neither the Commissioner nor the Director of the Center are in a position to make a decision on an imminent health hazard. Only the Secretary of Health and Human Services has the authority to make that decision.

So the Food and Drug Administration, in essence, is a recommending body at this point, not a ;decisionmaker.

So that's where it stands at this point, at this moment.

Dr. Lassiter: In layman terminology, this is the

Center's evaluation of the petition filed by...

Mr. Frappaolo: The Natural Resources Defense Council. We reviewed it and this is our response to the Secretary with recommendations as to what she should do...

Dr. Lassiter: It can only come from the Secretary.

Mr. Frappaolo: That's right.

Dr. Lassiter: Is there a time limit on her reply?

Mr. Frappaolo: Essentially, there is no time limit. Figures of six months have been thrown around a number of times.

Typically, the Food and Drug Administration tries to respond because of issues that come under the imminent health hazard in a very timely fashion.

So, at this point, we have no firm data when the Secretary may make her decision ... once the document has reached... So we're not sure.

Mr. Megown: Can I ask you one question?

Mr. Frappaolo: Yes, sir.

Mr. Megown: You said it went to the Secretary's office.

Mr. Frappaolo: At this point, all I know is that it's been forwarded to the Commissioner. I'm not sure whether it has gone to the Department or not.

Dr. Hoffsis: OK. Anything further here? Thank you very much.

Mr. Frappaolo: Thank you.

Dr. Hoffsis: Next on the agenda is a discussion by Dr. Bill Jenkins, and the topic that's listed is a slight error on the agenda, and it will not be a discussion of what's listed there, but rather what we had asked Dr. Jenkins to discuss, and he's happily agreed to accomplish, is a discussion of the science of antibiotic resistance and transfer of resistance and plasmid-borne resistance, which seems to be the central issue of low-level antibiotics.

Dr. Jenkins is a pharmacologist from Texas A&M, who has expertise in this area, and if I'm not mistaken, he's also the incoming president of the Academy of Veterinary Pharmacologists and Therapeutics.

So we're happy to have him on our Committee. And looking forward to your comments, Bill.

Dr. Jenkins: Thank you. When one's confronted with a problem such as this, one can undertake indomitable Aggie ingenuity, and solve the problem very easily in such a fashion.

We are, however, dealing with an issue that is not such an easy solution to, and this indeed is Scott Holmberg's paper, which was published in the New England Journal of Medicine -- it's a little out of focus on this side and a little bit of focus is on this way.

Let me just read it to you then. I just wanted to emphasize one or two points in the summary statement. The one is, "Any persons who are infected with the Salmonella newport that was resistant to ampicillin, carbenicillin, and

tetracycline, carried throughout by a 38 kilo base of plasmid." So there is a facet of that resistance that I want to emphasize or at least explain to those of you who aren't familiar with it this morning.

Then it concludes, "The study demonstrates that any microbial resistant organisms of animal origin cause serious human illness, and emphasize the need for more prudent use of antimicrobials in both human beings and animals," and they underscore that entirely.

But it clearly is a monumental problem that has been with us for some time, and I use Bronowsky's quote advisedly here, "All information is imperfect. We have to treat it with humility, that is the human condition."

So the information that we have available and much of which I'll discuss with you this morning is not perfect by any manner or means, but I'm going to try and emphasize the current understanding of the mechanisms involved in antibiotic resistance, and perhaps emphasize to some degree the transfer of this resistance from one bacterium to another.

And it is time, really, to make an apology. I'm well aware that there are many of you that are microbiologists. There are also epidemiologists. I am but a humble pharmacologist.

And I present this, then, in a pharmacological context in a very general fashion, so that as this issue, which is going to be in front of the Committee for some time, I have little doubt of it -- not necessarily the low-level feeding of

pennicillin and tetracyclines, but there are going to be other facets that are going to be brought to our attention, but at least the terminology, we'll be comfortable with the terminology, and perhaps more importantly, understand some of the mechanisms involved.

So that's my goal today, is simply to review what antibiotic resistance is and indeed how it may be transferred. And there are very different terms used for antibiotic resistance.

We speak of natural resistance and acquired resistance, which are two very general statements which need some definition.

We speak of chromosomal and extra-chromosomal resistance, the chromosomal having the determinants on the chromosome, and the extra-chromosomal determinants then on the plasmids.

And I'll point out to you later on that that's even spurious, that effective codons may be interchanged as free transposons.

It's microbiological antibiotic resistance, which is the term we've been using equally so. Clinicians, though, speak of resistance when one of their cases is unresponsive to treatment, recognizing that clinicians never make a mistake in diagnosis. So it couldn't possibly be the cause in that.

Mechanism of acquisition, then we speak of selection of resistant clones, their mutations, and I'll say a little bit more about mutations later. Transduction I'm going to say

something about and R factors.

And then, of course, at the biochemical level, the exploding body of knowledge in biochemistry today. We speak of the destructive enzymes, and I'll concentrate on beta lactamases, various to penetration, and altered enzyme specificity.

And this is then at a biochemical level, so the term antibiotic resistance has become a very generic term, which encompasses a great deal of broad and some very specific aspects of this very real problem.

The first thing I thought we needed to address, and I apologize again for the simplicity of this, that is why do antibiotics exist? Are they a new creation?

And I must point out the obvious, that antibiotics are a very, very natural phenomenon that have been around for a long time in a mixed culture such as this, which is a yeast, a micrococcus with a few Bordetella thrown in, that these are not happy bedfellows.

In fact, they dislike each other intensely because they're competing for energy sources, and for that reason, have gone about the business of doing each other in, in one way or another, to become survivors of the fittest.

Now we see some of the effects here. A group of staphylococci, they can't separate from one another because they've been affected by antibiotics produced by other bacteria, fungi or whatever the case may be.

There are some other effects we see so seriously impaired here and undergoing lysis. They may explode presently, but they certainly are severely disrupted. Now we see inundation of bacteria, and they are most uncomfortable and going to survive too long. I mean the body host leukocytes will quickly attend to them.

And of course, it may be devastating for a bacterium, whereas where an antibiotic may have such a pronounced effect that we get rupture of the cell wall, and that's the end. Lysis occurs.

So first we have to recognize the fact that antibiotics are natural compounds produced by microorganisms affecting other microorganisms, and the next key feature is not in the same way.

They, in fact, bring about these effects at various sites, and I don't want to go through all of these. I just want to point out where much of my thrust will be this morning.

There are the cell wall synthesis inhibitors. We'll speak about the penicillins and cephalosporins and some of the other beta lactam products like that.

But there are other antibiotics, such as bacitracin, which has been used in feed for years, which also affect cell wall synthesis.

It is possible for antibiotics to attack on the DNA structure. We see that with novobiocin and maladixic acid, which interfere with the separation of those DNA strands.

Rifamycins, a newer group of antibiotics, newer from the clinical point of view, interfere with DNA dependent RNA polymerase so that separation of these strands becomes difficult, and the organism ceases to grow in many ways.

And we get the protein synthesis inhibitors at the thirty S ribosomal level, which is there, and here we have the tetracyclines and the aminoglycosides. Spectinomycin is an aminocyclitol drug -- affecting that thirty ribosomal level.

So we have a ribosomal effect at one of the substructures, or subunits, and at the fifty S subunit, which is the other part of the ribosome. We see that the macrolides and the iniquitous chloramphenicol exert their effects in impairing the genesis and formation of peptide linkages.

We have the cell membrane effects produced by the peptides, and I'm not going to say anything about them any further.

And then it is is possible for antimicrobials, that sulfonamides and trimethaprim (not antibiotics by strict definition; they're not produced by microorganisms), in fact, are able to inhibit metabolic pathways.

So we have several sites and several mechanisms by which antibiotics can attack and destroy and disrupt the function of a bacterium or microorganism.

And why does resistance occur? And the answer now is easy, that the attackee, or the victim, has got to do something about survival.

So we have the antibiotic resistance developing

within organisms simply to protect themselves as they struggle for survival in a very competitive world.

So we come to various forms of antibiotic resistance or antimicrobial resistance, and I want to spend maybe 10 or 15 minutes pointing out where and how this resistance can develop, and then we'll come to the mechanisms.

There are several types of phenotypic resistance that can occur, and the first one has to do with the permeability of cell walls. Especially gram negative cell walls are very complex structures, and it becomes obvious that an antibiotic has to penetrate a bacterium to have an effect on any of those sites I've pointed out.

Now this occurs down narrow conduits which are often called porins. I thought that would be a good name for a bar sometime, a Pour Inn.

This is what a structure of a cell wall looks like then, and notice these pores. Gram negatives are much more complex -- some of this is a little out of focus. I'm going to see if I can do better than that. David, could you just see what can be done, unless my eyes are giving me trouble, that doesn't look in focus to me.

That's much better. Thank you. That's fine for me. I hope it's OK for everyone else. Thank you, David.

So we're at the cell wall and then these porins are there, and it turns out that the water-soluble antibiotics have to diffuse down those pores, the lipid-soluble antibiotics can

penetrate the more lipid components of that particular bacterial cell wall, and it also turns out to be the case that sometimes these porins or these conduits are simply too narrow for antibiotics to diffuse through. And we see that very commonly. Pseudomonas is a good example of a bacterium with very narrow porins, so that many antibiotics can't penetrate through the more hydrophilic or water-soluble pores.

So this is a form of resistance where you get narrow porins, and it's a permeability barrier. Recognize, however, that there's an enzymatic component to this.

When you consider the resistance, I'll point out that each of these have an enzymatic or proteinacious component that is involved.

Well, what about the absence of cell walls, as we have in mycoplasms and then in some forms of bacteria called L-forms, which are protoplasts and shperoplasts, and in this case, with a group of antibiotics which attacks the cell wall and brings about disruption and lysis.

Well, if a bacterium doesn't have a complete cell wall, as we have with a shperoplast, or which has no cell wall at all, as we have with the protoplast, whether its cell wall synthesis is inhibited or not is irrelevant, because it's going to survive anyway, provided the environment has the same osmotic pressure. And in the body, that turns out not to be very common, just in the medulla, of the kidney and a few other spots where a hypertonic environment will protect such L-forms.

The pathogenicity and clinical importance of L-forms is still an unresolved issue, but it is a form of resistance.

What about changing target sites? As we looked at our sketch, we saw that antibiotics attack various target sites within the cell.

What about the target sites? And there are, in fact, binding sites that are very, very explicit, important and selective.

If we look at the beta lactam antibiotics, the penicillins, the cephalosporins, the monobactams, and some of the newer groups, they bind with very specific proteins called penicillin-binding proteins, not very original, but it is what they're called.

And then along the cell membrane here are the binding proteins that are part of the enzyme system that makes this peptidoglycan layer which bacterium needs in its cell wall, and we get beta lactams, amoxycillin as an example, but the same things with cephalosporins and others, which may come down that conduit or if more lipid soluble, directly through the wall, and they interact with those binding sites which are enzymatic-active sites, and what could be a form of resistance in them simply that the binding on those sites is not specifically selective.

We see this with, oh, several of the beta lactamase-resistant penicillins that have no effect in gram negative organisms, oxycillin being an example of that.

They will penetrate the sites with the affinity for the penicillin-binding proteins is so low, they have no effect anyway.

So we get that alteration of a binding site. The thirty S ribosomal site, which is an important one for streptomycin resistance (because streptomycin's role in medicine is dissipating fairly rapidly now). The thirty S ribosomal binding site is where the aminoglycoside then interacts with this thirty S ribosome and that thirty S ribosome in turn has to link with the fifty S ribosome, so that they can bring about protein synthesis.

But if you have an aminoglycoside involved in that thirty S ribosome, the protein that is produced is defective, and therefore, the organism ultimately dies.

But the point that I'm trying to make is we have another target site, the thirty S ribosome, and can that target site change? Can that specificity change? Can that receptor change? And the answer is indeed yes. In fact, in one mutation, in the case of streptomycin, it can be a single-step mutation where resistance can occur.

So there's another target site where resistance can develop. Then we come to the thirty S ribosome or the fifty S ribosome binding site, then we have the macrolides and the lincosomides, where exactly the same situation occurs. We have the fifty S ribosome there and we get binding of the macrolides and the lincosomides to that fifty S ribosome, and can we get a

change in that receptor so that resistance develops? And all of you know the answer to that. It indeed is the case again that by modification of that receptor site, resistance indeed occurs.

We see it with erythromycin, for example, and we see it with other macrolides.

Another target site effect is seen with sulfa resistance in one respect where in the presence of sulfonamide, we sometimes get an increased production of paraminobenzoic acid, an enhancement of an enzymatic effect, if you like, and a decreased enzyme affinity for the sulfonamide.

I'll come back to the alternative with you in a minute.

So that instead of successfully competing with paraminobenzoic acid, there's so much paraminobenzoic acid, the sulfonamide inhibition of an enzyme, the dihydrofolate synthetase, which makes folic acid, does not occur.

This is indeed not a factor. Equally so, the receptivity of that enzyme for a sulfonamide may be modified, again in its....

And this is an important one in the destructive enzymes, and now we're getting into several classes where we're speaking about enzymes that can destroy antibiotics directly.

And one of the better known ones, which we used to call the penicillinazes and the cephalosporinases, which today we call generic beta lactamases, are a group of enzymes then

which are produced by gram-negative and gram-positive organisms. The gram-positives are usually outside the wall in large quantity and they will destroy an intentionally harmful beta lactam antiobiotic, such as a penicillin G. Equally so in the case of gram-negatives. They're in a periplasmic space there usually.

So that any penicillin or cephalosporin that arrives is quickly eliminated by that enzyme. So here we have enzymes which actually destroy those antibiotics that are present.

And in most cases, they the beta lactamases simply because they cleave the beta lactam ring. This is the case of cephalosporin. So here we have a cephalosporinase which simply cleaves the bata lactam ring and as such, a structure without an intact ring is not effective and will not interact with that penicillin-binding protein that I spoke of earlier.

Beta lactamases, and I'm going to concentrate on them just a little bit to point out that this is not as simply as I'm perhaps making it this morning.

There are six types of beta lactamases, which are classified, as you'd expect, type 1 to type 6, and their substrates are different. And that's important. You'll see type 1 is principally active against cephalosporins, whereas there are other types that are effective against penicillins and cephalosporins, and type 6 is, in fact, against cephalosporins and penicillins.

So they are a whole family and indeed this is

simplicity itself because there are subclasses of these beta lactamases.

See here's another way that we can get antibiotic resistance. We can have enzymes produced by the defending organism which will simply destroy the attacking antibiotic produced by the other microorganism in its vicinity.

I want to just emphasize a few points here. I'll come back to them later on.

In the case of gram-positive bacteria, the beta lactamases here are usually outside the cell wall, and they are quite well carried throughout, and are excreted in the external environment, are produced in large quantities. They are mostly plasma mediated -- we'll come back to those in a minute -- and they are usually inducible, and I'm going to emphasize that point.

Let me do it now, and I'll do it again later because it is important. These enzymes are not necessarily there all the time, but in the presence of an antibiotic, they may be induced and produced in larger quantity, and then that's an inducible enzyme, which is often plasma mediated.

Or they may be constitutive, that, in fact, Staphylococcus is always producing beta lactamases anyway. It's a constitutive part of the life style, if you like, that they are producing those defensive enzymes, active against penicillins and unable to initiate self transmission is important. I'll come back to that later on. That means that

although it's plasma mediated, they may not be able to conjugate with another organism. I'll point out the significance of that later.

The gram-negative beta lactamases, just to emphasize a point, as I told you, are in the periplasmic space and not outside the organism, usually.

They are heterogenous very often, are produced in much smaller quantity, and they don't have to be produced in larger quantity. They're right at the site of the attack, so they can defend much more successfully instead of being in the environment.

They're often constitutive then, or chromosomal in origin, less often inducible, but they can be inducible in the presence of low levels and very often they are not able to initiate self transmission, and I'll come back to that point later on.

The aminoglycosides, there are several forms of resistance in aminoglycosides, in effect three major forms.

One of them is, again, and we're dealing with enzymes now, organisms that are capable of producing specific enzymes, which in this case, instead of cleaving the antibiotic will add a substrate onto it.

It can either be an acetic acid, acetyltransferase. It can be adenylaze, an adenylation occurring, nucleotidyl transferase is usually adenylation. Or it can be a phosphorylation.

So there are three enzymes there which are capable of adding a moiety onto the aminoglycoside, and that's the end of the aminoglycoside.

So it's another good protective mechanism that many organisms have against the aminoglycosides.

Chloramphenicol crops up again, always seems to crop up, and it has an enzyme, chloramphenicol acetyltransferase, which again transfers the acetic acid group onto the chloramphenicol and inactivates it.

So in a nutshell then, we have enzymes with two proteins which can be produced and may be in a defensive mode then and protective against antibiotics produced by other microorganisms.

Another form of defense is with the so-called carrier systems. We spoke about permeability, but it turns out that antibiotics are often actively transported into cells, the aminoglycosides are very water soluble and they have to be specifically transported into cells.

Tetracycline resistance is just the reverse. Tetracycline codes for transporters that heave tetracyclines out of the cell as quickly as possible, and that's what tetracycline resistance is all about.

It is not enzymatic. It is not a permeability. It's none of those. It's not metabolic, but, in fact, it's an activation of a reflex mechanism.

I'm going to use the aminoglycoside example, where

aminoglycosides then have to be actively transported into a bacterium, into a binding membrane associated carrier, and that transporter is very important for moving that aminoglycoside into the cell.

In fact it moves it in such large quantity that the aminoglycosides disrupt that cell membrane, and it's another mechanism of action that they have.

Well, what happens if we change the affinity of the aminoglycoside for that transporter? That is a form of resistance where the cell then doesn't receive all or the transport of the aminoglycoside into that cell no longer occurs.

And finally, the metabolic pathways -- and these again I emphasize are not antibiotics but the trimethaprim and the sulfonamides. It indeed is possible that alternate metabolic routes may be developed.

In fact, in the case of sulfonamides, the organisms can learn to use folic acid -- they don't learn, they have the enzymes to use folic acid -- instead of making their own folic acid, they use preformed folic acid, or in the case of trimethaprim then, a metabolic pathway will develop that will allow them to use folinic acid, or tetrahydrofolic acid, instead.

So in the case of sulfonamides and trimethaprim is metabolic inhibitors, it is possible for them to use alternate pathways.

Well, that's marvelous. Now, we've done exactly how

microorganisms in effect here can defend themselves against antibiotics.

The important question then is, is this just a single property that they possess or can they share this property with other bacteria?

And that's the issue at stake.

This is a magnificent representation of a bacterium, with its cell wall and its membrane and then its chromosome, and then its extra-chromosomal plasmid, and this is -- we're going to see this sketch one more time a little later on -- but here is the DNA sequence then. Here is an extra-chromosomal DNA sequence. There may be other plasmids. There's just one in this sketch, and we have to recognize that of all those mechanisms I gave you, they all depend either on protein synthesis or enzymatic mechanisms, and both of those are then produced by the activity in standard protein synthetic mechanisms or pathways are produced coded by either plasmid or, commonly, chromosomal DNA.

So we now have to look at the issue of how can this DNA strand, or that DNA strand, change to transfer or to facilitate the resistance of a bacterium.

There are two basic forms that we need to recognize, and these are just to get into a mode here of some definitions.

There is mutational resistance and transmissable resistance. Now mutants, there are always mutants around. It depends on the concentration of 10 to the minus 6 to 10 to the

minus 9. There's always one little bacterium that's different, and a mutant can emerge in the absence of antibiotics.

There are mutants out there all of the time which may be resistant. An antibiotic doesn't have to be present for them to emerge as mutants. It's simply a genetic failure, and then you take, and then under antibiotic pressure, where all the brothers and sisters are annihilated, they may then emerge, because they are not affected by the antibiotic.

And that's mutational resistance, which is something nobody can do anything about. It's a natural phenomenon that's going on all the time, simply through the genetic process.

Transmissable resistances then, where organisms have the capability of transferring DNA material, genetic sequences, from one organism to the next.

And how can we do that? We can do it, one way we can do that is by having enzymes, or coding for enzymes, that are protective, and I just want to remind you, again, that these may be constitutive or inducible.

They may be present and produced all the time naturally, or in fact, in the presence of antibiotics may be induced and produced in larger quantity. That's one of the facets of low-level feeding. That's where it can occur.

There are three forms of transmissable resistance and our whole focus, and indeed, often is on conjugation, and I won't argue for a minute that it is important, but I wanted to emphasize that there are three type of transmissable

resistance.

Transformation is the first. Transduction is the second. And conjugation mechanisms are the third.

In transformation, it's not very spectacular. It occurs principally in gram-positive bacteria, usually in vitro, but it could perhaps occur in burn wounds and in other wounds, where naked DNA simply diffuses through the medium from one organism and is accepted by the second or recipient organism.

And that is transformation, and it may not -- I hate saying this, because it's not absolutely true. It is perhaps of more importance as a laboratory phenomenon, and perhaps in superficial wounds. But that doesn't mean to say it may not occur at other sites. But it's simply the diffusion of naked DNA from one organism to the next.

Transduction is a lot more important than we have recognized in the past. Transduction is a mechanism that DNA moves from one bacterium to the next, not in the naked form, or not by conjugating mechanisms, but using a bacteriophage, where a bacteriophage then will infect a bacterium with a DNA sequence which then as more viruses are formed within that bacteria will accept some of the genetic material that confers resistance, leave the cell, and infect another bacterium.

So transduction, or phage-mediation, is where the DNA sequence is picked up by a bacteriophage in appropriate

resistance sequence and transfered to another bacterium.

Now it turns out to be important in several organisms, but Staphylococcus aureus resistance is phage mediated. It is an important form of resistance in Staphylococcus aureus.

But the one that I really wanted to emphasize, the one spelling error I have, believe it or not, is there, and that's the whole focus of this. It's R factor and not L factor but I suppose it happens in the best of families.

In fact, when we're speaking about conjugation, it's plasmid or R factor mediated, and I wanted to point out some of the features here.

We need to speak about some of the properties of these R factors, bring you up to date on what is known, and I need to say something about transposons, because they're a very, very important aspect of this whole scenario.

There is then a diagrammatic sketch of an organism and there is what's going to be a recipient. And the two features of this organism, I want you to notice, there is its extra-chromosomal DNA and its mostly green, but there's a little yellow piece in there.

That organism doesn't have anything and this has an appendage there, which we're going to call our sex pilus in a moment.

And this is what a plasmid or R factor really, or how it is made up. Somewhere on that R factor there is a sequence

of resistance genes and, as you just heard, it's very rarely for a single antibiotic. In most cases, it is for several, up to eight and perhaps nine, as well as other potentially harmful substances, such as mercury.

So we have these resistant genes in a sequence, and that little yellow piece we looked at is called the RTF for resistance transfer factor, and I'll point out its importance in a moment.

And then there's another region which sometimes is, its function is not clear, but again, as was pointed out, very often some of the virulence factors (the adhesion in the production of enterotoxins in the case of E. coli) are in fact on the sequence, or in that component of the plasmid sequence.

So this is a representation of a plasmid now, and as we watch these two bacteria perform, we notice then that this bacterium is capable of linking with that recipient bacterium, the plasmid opens up, we get the fusion across, we get it delivered into the recipient bacteria. I'm coming back to that. That's not perhaps totally true as I have it there, and I'll elaborate on that presently.

We then start getting division, and lo and behold, we now not only have a recipient bacterium, but very soon we have a family of bacteria that carry that very plasmid then, and they don't only carry the plasmid with the resistant gene sequences on, they also carry the RTF factor.

You'll notice that they now have the sex pili

whereas in this case, the sex pilus has been lopped from the organism.

So we now have resistant genes and the ability to conjugate carried in that recipient.

This is a plasmid. In fact, it's two forms of plasmids. This called closed sequence, also called a super plasmid occasionally. This is called an open circle. And recognize then that these are DNA sequences all along there, so as you noticed in the New England article, it's given as a kilobase number, and these plasmids then are characterized by the number of nucleic acid sequences they have or defined by the molecular weight of their ... They're either given in terms of daltons or in terms of kilobase sequences as the case may be.

So, we have several forms of plasmids, but this is what they look like, and in fact, here, instead of diagrammatically, is the linking of two organisms, where we have a daughter and a recipient and a sex pilus then in place.

This is another important point. In your reading from now on, you'll often see that a plasmid has a conjugative sequence or is non-conjugative. What that means is that resistance transfer factor or a factor is present where it will encode for conjugation, or is absent. So you can, in fact, get plasmids with the resistant sequences, but they're not capable of being transfered because they're not capable of conjugation. They're missing the RTF factor.

So in your reading, and I'll show you three examples later on -- when you speak of conjugative and non-conjugative

plasmids, it means that some have the intrinsic adherent sequence to bring about transfer or they may not.

And that's the RTF then, which may be in plasmids, and at another time, you'll run into R determinants, resistance determinants, and these are the little sequences that determine resistance, but they don't have the F factor. All determinants don't have the F factor.

Sex pili, I've spoken about. This is a very new concept today, of sex pheromones, and I'll show you in a moment what probably happens when bacteria conjugate, and it may be that these sex pheromones bring bacteria together, and then they're sticky enough to stick together for a while, that the exchange of prominent material takes place.

So we get cell-to-cell contact, and let me show you the two possibilities. This has been the thinking for many years, that is, you saw diagrammatically earlier, we give an unravelling of the sequence, and by various mechanisms that have been proposed, is actually transported down the sex pilus and delivered then into the recipient.

That is what we have thought for many, many years, and indeed it may still be the case. However, the current thinking, the current science suggests, in fact what this F pilus does is to bring these bacteria together -- it actually contracts -- to bring it together, to bring them together into close apposition. Then we get the unravelling and the delivery of the genetic material from the donor to the recipient, and

start ... division taking place, and a propagation of a sequence then or a series of bacteria that contain that R sequence.

So as far as F pilus transfer is concerned, it may be down the pilus, perhaps more likely it is appositioned like that that brings about the transfer.

The other important feature I wanted to bring to the Committee's attention is what are called transposons. Now, I said to you earlier, we speak of chromosomal resistance or plasmid mediated resistance, which is wonderful, but unfortunately these lousy little sequences don't stay in the same place all the time.

They, in fact, can move -- a sequence can move from a plasmid back into the chromosomal sequence, and sequences in the chromosome can move back into the plasmid sequences, so they undergo transposition, and the term we then use is transposons.

And this is a whole new field in antibiotic resistance, called transposons. They disappear, you see. You can isolate a plasmid and those resistant aren't there, and you culture a little while later or reintroduce them into a bacterial sequence and this resistance appears again.

And the question has been, where has it been? Well, we now know that we get this transposition of genetic material between chromosome and plasmid. So we have transposons to worry about.

And so we see transposons are being characterized, this is by molecular weight. They contain up to 120 genes conferring resistance. They can transfer from plasmid to plasmid or from plasmid to chromosome, so we get transposons moving all over the place as well.

And virtually any gram-negative bacterium is vulnerable to beta lactamase transfer... and that's specific for what...

So R plasmid mediated resistant... move towards the conclusion of this.

R plasmid mediated resistance is then the ability to, by using that DNA sequencing and coding, to develop enzymes specific, perhaps, for the target antibiotic, the beta lactamases, the beta lactams in this case... The acetylation of chloramphenicol by an enzyme. We may change the ability of tetracycline either to enter, or more importantly perhaps, to remove it from the cell so rapidly it has no effect.

The aminoglycosides might undergo enzymatic alteration. In fact, they have other resistant mechanisms as well, as I pointed out, associated with being transported into the cell.

Or we may get structural protein changes, all coded for those genetic sequences.

Now the other thing, and that's the same theme, except I wanted to re-emphasize that on these resistant sequences, there are other things like mercury which undergo

destructive decomposition, and there are other heavy metals which also are protected against, and you understand that in nature that it would occur, but they're also protected against by the presence of enzymes that would protect the bacteria.

There are many bacteria which contain R plasmids, very often the enterobacteria, as well as others which contain R plasmids, and then several gram-positives. But again, I must point out that in Staphylococcus aureus, which is an important resistant organism, it is not conjugation but, in fact, transduction which is responsible for the transfer of resistance.

But there are other gram-positives that are capable of conjugation.

So there are a host of bacteria, and this is the kind of table that we're going to see in our reading from now on, and now I hope it makes sense to you.

When you see a plasmid listed, and it has a number and a code sequence, then that means, as was pointed out earlier, that that plasmid's been characterized. It's the antibiotics against which it can code for resistance, its size and its other properties, biochemical properties, are recognized, and then those working at that level, at that molecular level, give them codes and numbers.

And we'll see RSF 10-10, using genetic coding, it codes for resistance. The sulfonamides and streptomycin, their plasmid is not capable of conjugation, of developing a

sex pilus, and its size is about 5.7 million.

So they characterized, and this again, as you've heard mentioned, now it's possible to follow plasmids because you can characterize these plasmids. You can... just take another one. Here is R-1, which is the Salmonella... is the way it's found. It doesn't still have to be there, of course. Sulfonamide, streptomycin, chloramphenicol, ampicillin, and in this case, that plasmid is capable of conjugation and it is a much, much bigger plasmid, as you would expect with a greater number of R factors on it.

So this is the kind of table you will see, and what those working at that level will look at, and then tables get bigger and bigger, and we could have gone on and on, but again you see that incompatibility group with the plasmids, you can't have the same plasmids, identical plasmids, in the same cell.

There's a phenomemon called incompatibility. There's only one plasmid of its type in a cell. The other plasmid is eliminated by it. They don't have to still be in the original bacterial host, and we see they're rather conjugative or non-conjugative, and we see the sequences, and in this case, again, it's in terms of molecular weight. It may be in kilobases, though, as you look at plasmids, they may be characterized in kilobase numbers.

Equally so, though, and I spoke of the transposons, transposons are being characterized today, because when they

break away in the DNA sequences, they break away intact. So we have TNL1-2-3. It's a beta lactam then, the resistance confirmed.

There is, that's another one, TN-4 and its resistance are transposons. When you look at, read in the field, you'll notice transposons have their individual characteristcs and numbers today.

So, conjugation transfer, the importance thereof -- we heard earlier we can get transfer from non-pathogenic to pathogenic strains. It can occur across species very readily from E. coli to others. We get multiple gene transfer and we've emphasize that enough.

It's perpetual because we saw in that little diagrammatic sketch how the daughters all were happily producing their plasmids, confidently and repeatedly.

And then the other point that I needed to re-emphasize with the virulence factors or the pathogenic factors are often carried on those R plasmids as well.

Clinical relevance is what I'm going to say very little about this morning. Enteric infections are problematic. Because of that, the use of low-levels of antibiotics have tended to bring about the emergence and, in fact, the misuse of antibiotics, indiscriminate use of antibiotics, in human hospitals, as well as out in veterinary practices, where we get indiscriminate use, these R factors do emerge. There's no question they emerge, and their significance and impact is

what is up for debate at this time.

Remember one thing, though, that plasmid-carrying bacteria are at a selective disadvantage. There's enough evidence to at least make this as a general statement that in many cases once they've acquired these extra R factors, they don't compete as successfully, and with time R factor-carrying bacteria do disappear from populations, and this has occurred and has been shown to be the case in England.

So if the, we see the same thing with mutation, just in passing. Sulfonamide resistance was very prevalent just shortly before the Second World War. The antibiotics arrived. Sulfonamides were used much less. So that mutational resistance with time then disappeared.

So we do have that on the plus side.

There are four other forms of resistance that I just wanted to mention because they are pertinent today. There's a term that you'll run into, tolerance, and tolerance has a very specific meaning, perhaps today in Staphylococcus aureus, as we see those cell walls with those penicillin-binding proteins, or transpeptidases, as we're making walls, or as the bacteria are making walls, at the same time they have to do a little architectural management and clean out some of the peptidoglycan strands that are in the way, and autolysins cleave out those newly formed strands as others are made.

And it turns out in some bacteria then, there is a diminition or absence of autolysins. Although you may interfere

with synthesis, there's no destruction taking place, and those organisms survive, and that's called tolerance. It's a specific form of resistance which you may encounter in your reading.

Persisters as they're often called. Persistence is where you may treat a case for a period of time and all of a sudden the same organism may emerge. The current thinking about persisters is that they may be totally quiescent bacteria that are not multiplying, not building cell walls, not making protein. They are quiescent. The antibiotics then, no harm is done. The antibiotic is removed or clears out and those organisms then can remultiply.

So persisters, and persistence, is another word you'll run into.

These two here emphasize another form of resistance that you'll run into more in clinical journals than in microbiological journals, when we speak of conditional resistance. And this means that the environment is unfavorable for the action of the antibiotic. In an aerobic environment, the aminoglycosides are <u>not</u> transported into cells. Their carrier system that I showed you is dependent on oxygen. And that is why the aminoglycosides are not effective against anaerobes, because aminoglycosides have to be transported even to cells in large water-soluble molecules.

If they're not transported in, they're not going to

affect the cell. So a form of conditional resistance then is anaerobic environment where an antibiotic such as the aminoglycosides may not be transported in.

And another form of conditional resistance is the effect of pH. Again, I've used the aminoglycosides as an example. The higher the pH, the aminoglycosides are much more effective. The lower the pH, the higher the hydrogen ion pressure, the more water-soluble they are, extractor changes and their activity is reduced.

And we know this, that very often in severe acidosis, the aminoglycosides are not as effective as indeed they are in cases where there's not a severe acidosis.

You alkaninize the environment to a pH of about 8, there is a 60- to 80-fold increase in the activity of the aminoglycosides.

So, Mr. Chairman, we come back to a tree, only it's a different tree this time, with some maribow storh in the setting sun, as we prepare for lunch.

But I hope that I've at least served a purpose in introducing those of you unfamiliar with the terminology to some of the terminology, some understanding of the mechanisms involved.

I haven't addressed the issue, and I'm glad it's sub judice because I'm going to use that as my excuse, you see, I can't discuss it, it's sub judice.

But it is a complex issue, and that was really one of

my main, two main targets. One was to show you how complex it can be, and secondly, to just bring you up to date with some of the terminology, and a final apology to the microbiological purists. I apologize for venturing into your arena.

Thanks, Glen.

[Applause]

Dr. Jenkins: Would you turn those off? Thank you.

Dr. Hoffsis: Thank you very much, Dr. Jenkins. I've asked Dr. Jenkins to prepare a few exam questions, which we're all going to have to pass before we can have lunch, and as for myself, I had a large breakfast.

Does anyone have a question for Dr. Jenkins?

Dr. Jenkins: It's lunch time.

Dr. Hoffsis: OK, we're going to adjourn for lunch. We will reconvene promptly at 1:15. We'll meet just few minutes later, and we will amend the agenda again.

We're going to start with Mr. Gary Dykstra right after lunch, so he can get to a meeting, and then we'll go to our discussion items right after that.

[Lunch]

Dr. Hoffsis: As I mentioned before lunch, we're going to amend the schedule slightly, and to accommodate Mr. Gary Dykstra's other commitments, we'll get him on first to speak about the sulfa residue problem. Gary.

Mr. Dykstra: OK, thank you, Glen. This morning I was challenged a little bit on the illegal sale issue to find

the positive in what we're doing in that area, and as enforcement officials, sometimes it's very difficult to find the positive element in some of these things that we do.

With regard to the sulfa problem, it is sulfamethazine really that we're talking about. If you look for the silver lining in this particular problem, the only thing that we can say, in a very positive sense, and we say it every time that we talk on this issue, is that we believe it's a very small number of producers out there that are causing the big problem.

Again, the large number of swine producers, we believe, are law-abiding citizens. If given the opportunity to obey the law, they certainly will do that.

So here again, we're doing everything that we can to keep the honest folks honest, and we believe it's just a very small number that's causing the problem, and we're trying very hard to deal with that number.

As most of you recognize from the briefing that we gave you the last time you were in, we've been on a kind of a roller coaster with sulfamethazine.

It's been an up and down kind of a thing in that back in the late '70s, we experienced what has turned out to be an all-time high in sulfa violations.

And as a result of that, we put our heads together with other government officials and industry people, and came up with a very intensified and very comprehensive education

effort, because what our survey showed was that it looked like it was husbandry practices that were by and large causing the problem, not a lot of attention to how these animals were being raised prior to slaughter.

So we put that effort in, and as it turned out, it was well worth it. The violative rate came down, came down rather dramatically.

So everybody sat back in their easy chair and relaxed, and we thought we had licked the problem, only to find out that in the early '80s -- '82, '83 -- the residue rate started creeping back upwards again, and as enforcement officials and public health officials first and foremost, we began to get concerned again, and wondered whether people were just slacking off in the husbandry area or some new situation had presented itself.

So we began looking into it. We looked into it. USDA looked into it, and many State officials began looking into it.

What we began to see was a pattern of using cheaper sulfa products -- again, it's the sulfamethazine products. And these cheap products were available in a powdered form, still available in a powdered form, both in bulk and as a legal water-soluble product, which can be used illegally in feed, and perhaps at increased dosage levels.

There was a study done at Purdue University, which bore out our initial feelings about this situation, and they

discovered that, indeed, some of these producers were using that kind of a sulfa product.

I'll remind you again that the only sulfamethazine product that's legal for use in swine, in the feed, is a combination product, sulfamethazine plus other antibiotics.

As a direct result of these findings, the industry itself took the initiative last summer to convene two separate meetings to discuss the situation.

We were very heartened to see that they were taking a lead in this area and were just as concerned as we were about the situation.

Those discussions were attended by Dr. Crawford, and at those discussions, we pointed out that it seemed to us at the time the problem was the use of this powdered product, the fact that if a producer were using it, they probably were contaminating their machinery, as well as the yards and everything else, and they're really going to have a difficult time cleaning things up.

That was pointed out very graphically to them at those two meetings last summer.

As a result of those two meetings, industry went away and did a very good job of publicizing that fact, and they were telling the producers that if this is the situation and you're using this kind of product, you ought not to do it.

The American Feed Manufacturers Association did the same thing. They warned all their member companies that, don't

get involved with this kind of a product if you can possibly avoid it, because it's just going to exacerbate the problem.

After those meetings took place last summer, we continued, as well as USDA continued, to monitor the violator rate. The violative rate is the total number of samples that USDA is collecting of swine tissue divided by the violations, or the other way around, I'm sorry.

And what we noticed was there was no lessening of that violative rate. So we put our heads together again, and decided that we had to take more stringent action.

And what that resulted in was a determination that first of all, FDA could do some things, and second of all, USDA could do some things, and third, and also very important, that the industry could continue their efforts to correct this problem.

It's a three-way partnership.

What you'll hear this afternoon is, first of all, my presentation, but you'll also hear from USDA, Dr. John Spaulding, if it makes you happier. You'll hear what they're doing, what their program is, and you'll also hear from Dr. Van Houweling on what the industry is doing, what their perspective is on this problem.

After getting our heads together, we decided that we needed another meeting with all the involved parties, and we called that meeting, here at FDA.

And we notified the Committee that we were doing

that. We felt that we couldn't wait any longer. We needed to do something.

So we held that meeting on January 24th of this year, at which again the same parties were involved, government and industry, and we talked about the problem, quite a very open and candid discussion.

And we laid some options on the table, and quite frankly, we were surprised because the participants said that perhaps we were being a little bit too soft, and that maybe we needed to really have an intensified effort to search out the chronic violators, and get them out of the picture any way that we could.

So we took their advice to heart, and the program that we came up with, from FDA's standpoint, is a two-part program, and it consisted of a letter direct to the swine producers.

Now the purpose of this letter was to communicate directly with the swine producer. At no other time had the Federal government directly communicated with the swine producer.

And told them about the problem and suggested some things that they could do to crack that problem.

So we sent this letter out to about 114,000 swine producers producing more than 200 hogs a year.

The interesting thing about that letter was that we sent it out to a mailing list, which we had purchased, and it

was supposed to go to swine producers producing 200 hogs or more a year, and six of those letters went to the District of Columbia.

And we're still looking for those hogs down in D.C. [Laughter]

But I guess those kinds of problems happens with mailing lists.

Dr. Crawford: I think that's one hog in a syndicate of six.

?: Out there at Redskins park. [Groans]

Mr. Dykstra: In any event, the letter did issue. It issued on March 25th of this year. These things always take time to get together. This letter, I might add, was a really a letter put together by committee.

We solicited, we told the meeting in January that we'd like to do this. They thought it was a good idea, and we said, "Give us a -- here's a draft of the letter -- give us all your comments, and we'll do the best we can to incorporate those comments."

And we received quite a few comments, and we bent over backwards to incorporate those comments in the letter. And so the letter takes on a kind of that tone, I mean written by a number of different factions, and it was intentionally done that way.

The letter did three things. First of all, it told the swine producer that there is a problem. It told them that

we are serious about solving the problem. And third, and maybe most importantly, told him, provided him directly with specific information that they could use to lessen their chances of having residue.

And it was put together rather cleverly in that that information was a perforated tear-off sheet. So they throw the rest of the bureaucrat language away and keep the most important part, and hopefully they did that.

That letter again issued on March 25th. The program, what we decided to do after that was that we didn't want to just have simply a paper tiger out there, and we decided that we needed to follow that up with a program to get after those so-called chronic violators, and anybody else who might be sending violative animals to market.

And so we issued an enforcement program, which had some innovative approaches. We got together with USDA, who as you know does all the sampling of the hogs, and decided that we wanted to have a more rapid exchange of information on those findings.

So as soon as they found out that a producer submitted a violative animal, we wanted to find out, FDA wanted to find out, just as quickly as possible, so that we could get out on that person's doorstep, literally within days after that occurrence.

The residue program, the way it normally functions, sometimes it takes us months to get out on that kind of a

follow-up, for a variety of reasons.

So we really were pilot testing some new techniques here, as far as sharing information between us and the USDA.

The other thing that we felt was that if we could get out there quickly, people's memories won't have faded too much, and we may be able to get some valuable intelligence, and we may also have a direct impact on that producer, as well as his friends and neighbors.

That enforcement program has been in operation now since April 1, and we intend to keep it in operation until at least July 1, to see how it works and whether we have any impact.

That program will be followed closely, we hope, with a program initiated by USDA, which Dr. Spaulding will explain later on in the program.

Let me tell you now what we're seeing as far as residue rates are concerned for sulfamethazine in swine.

In January of 1985, the residue rate was 11 percent, as compared to 7 percent in '84.

In February of '85, the residue rate was 7.9, as compared to 5.4 in '84.

In March of '85, the rate was 6 percent, as compared to 6.4 percent in '84.

In April, the residue rate, so far, and these may be somewhat incomplete figures, but it was 5.4 percent. In '84, it was 6.5 percent.

So you can see the numbers jump around a little bit. At the end of '84, just to refresh your memories, the rate was about 6 percent, overall. Right now, we're averaging a little bit above that, and it's too early to tell whether or not our program, by itself, is having much effect on those rates.

The last thing I want to point is we are now getting some data in on our program, and I'd like to pass some of that data on to you, because I think it's informative and a little bit instructive.

We have residue reports now from Pennsylvania, one in Pennsylvania, one in Illinois, one in Iowa, one in Kansas, one in Nebraska, one in Georgia, one in Mississippi, and one in Texas.

So they're pretty evenly spread out.

The other thing that we fully expected to have problems with was the actual trace-back to the producer of these animals.

If you're at all familiar with the way hogs are marketed, there's a lot of co-mingling that happens, and animals are not always well-identified. They lose their identity and it's difficult to trace back on those animals.

So, out of these findings, we have only two good trace-backs to producers, and one of those is in Texas and the other one was in Iowa.

We have done those trace-backs, and we did exactly what we intended to do in the program. We were out there

within days of those findings.

The individual in Iowa apparently caused the residue by sheer carelessness in mixing his feeds. He was an on-the-farm mixer.

The inspection in Texas revealed that this individual did just about every illegal thing under the sun, as far as treating his hogs. Illegal combination of drugs, all kinds of illegal drugs themselves, perhaps failure to observe withdrawal times, just a very, very egregious situation.

The other piece of data that we're gathering through this program is the problem of animal identification.

This is something that we've been discussing both with Food Safety and Inspection Service at USDA, as well as the Packers and Stockyards Administration in USDA, and it's foremost in the minds of many industry groups, not the least of which is the American Meat Institute.

They have petitioned USDA on at least one occasion to have mandatory animal identification. It's something that, whose time I think is long overdue. I think we're going to get some good data out of this program to help bolster that issue.

That's all I have right now. If you have any questions, I'll try to answer them.

Dr. Hoffsis: Thank you very much, Gary.

Dr. Lassiter: Glen, since we serve quite a few hogs down our way, I'm not sure I should ask this, but do you know where these violators are? The big ones?

Mr. Dykstra: Where the big violators are? Other than the ones that I just ticked off to you, ...

Dr. Lassiter: Yeah.

Mr. Dykstra: I mean those are specific instances.

Dr. Lassiter: Yeah, yeah. That was only two farms.

Mr. Dykstra: What?

Dr. Lassiter: That was only two farms.

Mr. Dykstra: Right. But in our routine residue program, we're finding 20 to 30 percent able to trace back to the actual producer. Maybe I don't understand your question. You're talking about...

Dr. Lassiter: Well, what I'm saying, can you tell a State, you've got ten producers in this State that have got major residue problems?

Mr. Dykstra: Yes, we can do that. If we have good producer identification.

Dr. Lassiter: Well, I can just tell you the Extension Service in North Carolina will cooperate with you. ...going and talking to those people.

Mr. Dykstra: Well, yeah, that's the kind of thing that we want to do, and we've done it in other areas, and we want to pursue that sort of thing.

And certainly that was a part of our big effort back in '78, some of that kind of activity.

Dr. Lassiter: The other question I have is this illegal sulfa. I'm a producer, how do I obtain that? I don't

have any hogs.... Where do they get it?

Mr. Dykstra: Well, sometimes we wish we knew. We know that they get it. It's being bought through the illegal distribution schemes, if you will.

Sometimes they're from dealers. Sometimes they're getting it from veterinarians themselves. That's about all we know right now.

Dr. Lassiter: Are they using this in combination with an antibiotic or are they making their own combinations?

Mr. Dykstra: Sometimes they are. This individual in Texas is making illegal combinations. Sometimes they're using it straight in the feed at two and three times the dosage level.

Dr. Hoffsis: Bob.

Dr. Phemister: You described your two-part plan with plans up through the first of July. What sorts of things are you thinking about beyond July.

Mr. Dykstra: OK, in July, or shortly thereafter, what we intend to do is, of course, evaluate this program, and see if it was at all useful. Perhaps we'll have another meeting with the industry to present the results of that evaluation, and see what the next step is.

As I mentioned, one next step which is going to be taken, it's going to be taken by USDA, and Dr. Spaulding will describe that, and that is going to be a very stressful program for the industry.

I think it will have an effect if they put it in place.

Dr. Phemister: But it's not in place now?

Mr. Dykstra: It's not in place now. They're going through the rule-making processes to give everybody an opportunity to have a voice into that program.

Dr. Phemister: Is your target zero percent violation rate?

Mr. Dykstra: Well, some people say there's no such thing as zero. We would certainly like to see it significantly reduced.

The overall residue rate for all drugs is somewhere between one and two percent, and you know, we'd certainly like to see this get down to within that range, if at all possible.

Dr. Hoffsis: Elwyn.

Dr. Schall: While a sulfa ... is legal, the ... is three combinations.

Mr. Dykstra: That's correct.

Dr. Schall: But when you need sulfa, that form of sulfa costs from seven to eight times as much as the powdered that they're using. That's an awful lot of economic pressure.

Mr. Dykstra: Exactly.

Dr. Schall: Would the availability of granular sulfa solve some problems?

Mr. Dykstra: I think that would help solve the problem. The difficulty there is is that the manufacturer

would have to take the initiative to come in here and get an approval on that kind of a product.

Dr. Schall: Yes.

Mr. Dykstra: And, you know, that's where the manufacturers play a role in this problem. If they could, if producer groups could put a little pressure on those people to come in with that kind of information, maybe that would help solve the problem.

Dr. Schall: I would have to be competitive in price with the powder.

Mr. Dykstra: Sure.

Dr. Schall: And I think it would help a great deal.

Mr. Dykstra: Right. Any other questions?

Dr. Hoffsis: I think that we can take that as being no further questions for you. If you need to get to your commitments, fine.

Mr. Dykstra: I appreciate that.

Dr. Hoffsis: We will, at this point, take some discussion on the topics that we had this morning. Anything further on the low-level antibiotic issue, and anything on Dr. Jenkins discussion that we maybe didn't have adequate time to discuss.

Anything from the committee, first?

At this point then, there may be a few comments that we could take at this point from any one in the audience.

Dr. Bechtel.

Dr. Bechtel: I'd just like to ask a question... But at the United States Animal Health Association meeting in October... That was when the Holmberg situation, including..., and it was mentioned to us there in one of our committee meetings, that was not being used as data for the low-level antibiotic -- it was not being used as data, and yet ... it was one of the issues that the Commissioner is looking at. So I'd like to know...?

Dr. Crawford: What we do is a literature review, and it's in the scientific literature, so it's considered. You were, I didn't know you were informed that it wasn't going to be used.

Dr. Bechtel: Yeah, Dr. Gable, at one of our committee meetings, we were trying to come up with some kind of response, and he said, no, we don't need to, it is not going to be used.

Dr. Crawford: What he may have meant then, it wasn't a pivotal thing. In other words, it wasn't going to be decided specifically on that.

Actually, I believe there are, what, several thousand bits in the literature, right?

Mr. Frappaolo: At least. There's tens of thousands of citations.

Dr. Crawford: About seven thousand...

Mr. Frappaolo: ...And we said all along that there's no one study that we've ever looked at that we would consider

pivotal, as making the decision. ...the total body of evidence.

Dr. Bechtel: You just mentioned this morning ... seven thousand....

Mr. Frappaolo: Sure.

Dr. Bechtel: So, you're looking at all things.

Dr. Crawford: Yeah, and it has been one of the most, one that's mentioned in the news, sensational and so forth. So it's the one people think of, and they forget about the fact that there are other studies in the ... here, many of which show different things.

Mr. Frappaolo: See, with respect to the Natural Resources Defense Council's petition, they specifically cited those studies, so we had to respond back to them.

Dr. Crawford: And that's the difference between what you heard today and what your heard in Fort Worth. The Natural Resources Defense Council is based somewhat largely on the two Holmberg studies, so therefore we had to ...

Dr. Hoffsis: Anyone else? If not, we're going to go on to the next topic, rather than take a break, as scheduled.

[Unintelligible comments]

Dr. Hoffsis: We're still talking about residues and, particularly with respect to sulfas, and we're happy to have with us to speak about I assume sulfas as well as the whole residue problem, Dr. John Spaulding, with USDA/FSIS, and pleased to have you.

Dr. Spaulding: Thank you. I'm going to use the overhead projector, but before I do that I'd like to hand out to the Committee -- I brought the current, at Dr. Van Houweling's request, the current residue status.

The data is good up 'til May, because we've been running about 100 swine samples a month. So when you look at the bottom line, if it says 100, you say that data isn't going to change very much, maybe one or two samples either way.

The other part of the data that you should look at, in answer to the question -- I've got this on a transparency, but, I think -- but the other part of the data you should look at is you'll notice in swine sulfas, it's concentrated, as far as high violation rates, in the Southeastern United States.

I would not look at any individual state, because the number of samples is just too small to make any conclusions, but if you look at the Southeast and compare it to the others, you will find that the Southeast seems to have a slightly larger problem than the rest of the country.

Now, if you'll just put that aside, we'll get back to swine sulfa, but I wanted -- I knew you'd look at it when I handed it out.

And we might as well talk about what I call real-time data, and -- everybody talks about a residue problem. This is our yearly summary data on '84.

If I went back two or three years, you'd see the same pattern. If you look at this, you're going to find that we do

have a residue problem... We got one in rabbits over here, in antibiotics. The rest of it to me looks pretty darn good for the things we test for and for what the industry is using.

We do have a problem with antibiotics in rabbits. I'm the first to admit it. I wish I knew why they were there. Then we could do something about it.

Let's look at livestock. Livestock, if you look at the overall data, you'll find out that when effect impairs, again in antibiotics and sulfas, which took out a little bit of a problem that we've got to do something about. But we're working on it.

And I'll give you some more defined data. We also, as you all know, we got this little old troublesome problem in swine, and as Dr. Van Houweling has already accused me, we're going to use a 16-inch Naval gun that probably, with proper education, could be handled very easily by a farm boy with a 22.

But the thing is we have to get people's attention. Look at the rest of the data and it says really from residue standpoint, there is not that much of a problem out there.

Really what I'm telling you is of three residue rates that could be considered problems. There is one that we lack data enough to know how to attack it. There are two that we are doing something about.

And this is probably the most complete set of data.

Dr. Jenkins: Can I just ask about that chart? Cows,

chlorinated hydrocarbons?

Dr. Spaulding: Chlorinated hydrocarbons in cows, that's -- the percentage is wrong, if you look at it, and I can't help trying to train one of my educated Washington girls that graduated a few years ago in check.

But I'm glad you called it to my attention, because I'll call it to hers, and as they'll tell you, I would not want to talk to her about that later.

The thing is, what have we been doing? How have we been accomplishing all these reductions?

And really, I think Dr. Crawford agrees with me, that between FDA and FSIS, which are operating under different laws, we develop what I call symbiotic relationship.

We're both benefitting by working very closely together. As you know, and we are sometimes asked about this, and Dr. Crawford is asked also, where does our authority start and where does his end?

Our authority starts when the animals are presented for antemortem inspection in the pens on the premises. That's when FSIS authority starts.

We have absolutely no legal authority prior to that. And that's not always well understood.

The thing is that we have learned by working with FDA and working with industry groups, we can develop very good programs.

This is how the level of antibiotics in cows has

declined, and if you will look at the effort and working with industry started in '79 -- in fact, what I don't ... is we have fomented this out....

In about mid-'79, we adopted a very successful philosophy taught to us by our public health agencies, when the toboggan is going downhill, that's the time to get on it and ride it to success. And we've done that.

But the educational effort started the whole process, and the fact that we did have an in-plant test.

You say, well, what are you doing to maintain that? How did you keep it going down?

This is the number of in-plant tests for stock that we have been doing, year-in, year-out. Stock is on a different principle. We have, in effect, told our veterinarians to test those animals that in your mind you would have treated and sent to slaughter.

We're using veterinary diagnostic skill. We've given them an in-plant test that will allow a result before a packer suffers an economic penalty.

The fact that it has stayed around 10 percent, quite frankly, I'm pleased about because it means our people are not being too conservative in applying the test, and they are picking them out, and they are maintaining awareness on the part of industry that we are checking.

That sampling rate also illustrates another thing about in-plant tests. If you notice, we're running around

8,000 or 9,000 stock tests a year. Our total residue program using laboratory facilities is running around 30,000 to 40,000 samples a year.

And this test is a very small cost. It shows what you do when you turn them loose. This is the other program. This is the calves program. Again we talked with industry. Again we looked at and talked with the people involve, the dealers.

In '78, if you take that percent violations, you'd go from '78 back to when we ... kept records. And it will be at least that high, if not higher.

We've never been able, until we had an in-plant test. Now in the calves program, again we went into an educational effort, the R.A.P. program, in '84, and in '85 what we are finding out, we're going to have to modify our final rule to allow for flexibility in, when we're running the calves test, because it's getting good enough on calves' violations, that we can consider going downward in the number of samples that we're taking.

This is incredible data when you realize that along about 1.6 percent is the animals we condemn, and we're including in this program animals with disease conditions that are being condemned anyhow.

Between one to two percent of all going to slaughter are condemned for diseased conditions, and so when you subtract out that, which obviously ... in the high percent of being

treated, you see we have really achieved not quite as much as we did with cows, but we're sure headed that direction.

And a problem we had no handle with prior to that.

Now, as Gary said -- and I want to show you one other thing. This is the swine, and compared to the two previous charts that I showed to you, you can see that we just haven't really found the right approach to work with the swine industry.

And the level right now is, the data says, and everything is staying around this six to seven percent. It bounced up to 11 in January when the weather was bad. It's come back down.

In April, it looks like it's back down to five. It's probably because of the educational efforts, the letters that have gone out. The educational program has probably taken effect.

The thing is that we have talked and we developed and it was finally cleared and published on Monday, a Notice of Intent to Regulate. And the reason that we went this route is the program that we have proposed is probably the most severe residue control program that we have even discussed, and what we're telling people is do not doubt that we will implement it if we have to.

What we will do is hopefully get good suggestions, constructive criticism, so that we can develop a better program.

And this is what is in the Notice of Intent. A swine program consists of these steps. Swine are brought to the slaughter plants in a truck. From the truck, they move to the pens, ... pens.

They are then slaughtered on the kill floor, put in the cooler, and then from the cooler, they go to the cutting room and the chart of sampling that we put together for them is really the design of control.

What we're proposing in this program is that the lots we will sample are based on the truck arrival at the slaughter plant. In other words, a truck load of hogs, be they 6 or 200, we don't really care, because that we can identify.

And also I told you when they arrive on the premise they become under our jurisdiction. We will try to gain identity of hogs to feed information back to FDA, but this program is going to be working very quickly.

At the slaughter plant, and in the ... pens, we will provide an in-plant test to our inspectors. Currently, we're working on a sulfa on-site test that is chemistry and uses thin-layer chromatography as its base.

It's just a derivative of the AOAC thin-layer test we're using in our labs, but we're not trying to quantitate it, as we can in our labs. We are reading it against the standard, and say they're good or they're bad type of situation.

Animals, once they're in the pen, we will get the, we will select with bias the pens we want to test. You noticed I

said, "with bias." In other words, that's with the information we have available.

In other words, if we have information that we've got animals from a chronic violator or from a chronic source where they've been playing games with us, we will select those first.

Part of the reason I'm allowing "with bias" is I know of no way to stop our veterinarians from not doing it, and so we might as well approve it.

The pens of animals, we will select probably six animals out of that pen. They will be identified. The animals in that pen will remain identified, under suspect retention authority that we have.

The packer, quite frankly, has the option of leaving them in the pen until he gets test results in a couple hours or he can slaughter them.

I will never ... a packer. I would never answer for the headaches that would be encountered if I slaughtered them until I knew test results. I'll go into that.

Then the animals that are selected for suspect. We haven't learned how to collect urine from hogs yet without slaughtering them, so those test animals will go to slaughter. If we learn how to collect urine from hogs on antemortem, fine. If we get the blood so it works, fine.

The test animals that go to slaughter will be held under a retention, and also the ... We will run the test in the government office.

We will have results right now, based on the way we're rating the test. One positive result out of the six will be reason for condemnation of the lot of hogs.

Now when we say condemned, we do not mean put in the tank. That is our way of our agency saying they are condemned as far as we're concered, Mr. Packer, now you have some options.

You can hold them until they're depleted in your ... pens, or some other facility under government security, or if you have, you can, in effect, if the offal is bad, you can kill them and we'll, if the test says the offal's bad but the carcasses are good -- we don't know if we can read it this close, we hope we can -- you can kill them, the offal will be destroyed, but we will be based on laboratory tests for clearance.

And so the thing is the carcasses will clear all right, but if all this gets into the cooler, then the only option he has is individual testings. He cannot hold them on antemortem. He cannot hold for depletion.

The trucker that delivered, or the truck and the source identified will be tested until we're satisfied they no longer deliver hogs that are containing sulfa residues.

Now we also build into this program the option for producers, brokers, slaughter plants to furnish us information in advance that these hogs should be considered clean because they've met certain criteria, so that we can work with them.

In other words, we're trying to build in all of the options.

The program in the Federal Register, and I just brought a couple or three copies of it, really the way I look at it, this is one we wrote in Washington without knowing much about hogs and hog marketing.

And so I compared it to one or two people over the telephone in the last couple days as we have decided to go to Winchester, Virginia. We're going down Route 7 and we're walking. Now if you know a better way to get to Winchester, please tell us.

And that's really what we want is constructive criticism. We want input. Gary said that the letter they sent to producers was written by committee. Quite frankly, I would like to see a residue program of how we're going to work written also with good, constructive input.

The thing is that right now we're working with a sulfa test. We've got three options. Any one of the three we may or may not use. We have the chemistry test that is thin-layer.

We have people coming in, I think today, to talk to us about a sulfa ... card test. It's either today or early next week, that they think that we could use.

And of course we have the old standby -- Ralph Johnson is one of our wonderful brains, and his group. If you give him a problem, and is responsible to microbial testing,

Ralph will come up with a test.

Now he also has a sulfa test, but he hasn't been pushing it because he knows under the conditions, we are talking 18 hours for antimicrobial test, and that won't work in the system that we're dealing with.

And so the thing is really what I'm hoping is we will go through the Notice of Intent. We will get good input, and the fact that we are willing to do it, and we will put a proposal in the Federal Register, and then I hope we never have to go any further than that.

But that's not the question of, in our agency, never worry about whether about whether we will, once we start. The question is, do we have to? And we have always stopped when a need for "have to" disappears.

And so that's where we are. Actually, I'm very happy about the residue program and what it tells from residues. I'm glad CVM has the problem of antimicrobial resistance.

The thing is there are other subsets of our program , but within the time allocated and that fact that there would be questions, I really don't want to get into those. We can get into them later or at some other meeting, if you all have an interest, because we are working with industry in order to improve the controls. Again we depend on FDA to furnish this information. We depend on industry to tell us what is practical, and we're trying to put it all together, which makes life fun because every once in a while we make a mistake.

Thank you.

Dr. Hoffsis: Thank you very much. I think we ought to take some questions right now, if we have some time, and maybe we can work in a little break right before Dr. Van Houweling.

Dr. Van Houweling: Those are mine ... don't take those. Those are my transparencies.

Dr. Spaulding: OK, I will leave those.

Dr. Crawford: Let me have those.

Dr. Spaulding: One of the things, and I think that's wonderful, we all use our own data. Industry people finally feel free to call my office and ask one of my girls, what are you doing? Well, I'm doing some work for Dr. Van Houweling, ... over at the National Cattlemen's or something like that. I say, oh, go ahead.

We're all starting to work off the bases of data. We're all working toward the same end point. I just think it's wonderful.

Dr. Crawford: Thank you. Let me start by agreeing with John that we have the very best cooperation with FSIS, largely due to him, and also, if you notice, most of these slides that he has began in 1978 when we started working very closely together on the sulfa residue problem.

And I think you've proceeded from that point to where no country in the world can show figures like John has, and Johns's largely responsible.

Dr. Spaulding: Truthfully, I think the animal industry of today is such we ship any product anyplace in the world, and somebody says we're going to test it, I know our attitude's very simple, "Go ahead, and if you find anything, you're going to have to answer to us as to the test method, because we may or may not believe you."

Because they're using a lot of experimental methods that will not stand up to science. But if you find it, and it's there, let us know so we can do something about it.

And I think that we're the only country in the world with that attitude. We could care less whether they test our product or not.

Dr. Hoffsis: Dr. Lassiter.

Dr. Lassiter: Is this information private or public? In other words, can we use it?

Dr. Spaulding: You have not worked -- I'm not being sarcastic, it's just that those of you who have not worked in Washington offices do not understand we work under the Freedom of Information.

And as far as I'm concerned, not only would it be public normally -- I don't know how to protect anything in my office.

Dr. Lassiter: I just didn't want to sound like...

Dr. Spaulding: My standard, really, my standard response to people on Freedom of Information, if they want to see it, come on in, it's in the files. I refuse to go look for

it.

Dr. Jenkins: Can I ask a question? Your idea of selective condemnation of, say, viscera, in a case like that, is that novel or has that been done before?

Dr. Spaulding: It's been done before.

Dr. Jenkins: It has.

Dr. Spaulding: Our ... is an individual animal, piece by piece ..., so that we have got to, so that, in effect, the only question I've asked on this proposed program to our General Counsel is, will you assure me there is at least one animal with violative residues in that lot?

I said, yes. He said, condemn it.

And it's also a piece-by-piece, and so if you can separate it, I use that if you can separate it with a knife, we can test it individually.

Dr. Jenkins: That has some impacts on the aminoglycocides where we know we had kidney residues, but not in the rest of the carcass. I know that's not done, but it's a possibility for the future ... selectively condemn ...

Dr. Spaulding: We occasionally do it. In the case of calves, we are not doing it, primarily because there's no approved use in these little old calves with the withdrawal periods, and so we have just ignored that particular thing, and what we done, though, is we offer the packer the right to prove to us on an individual carcass basis that this carcass should not have been condemned.

Well, the lab test cost $50, the calf carcass is worth $20 or $30. And so he just looks at us economically and he says, you're not giving me any offer really, and you refuse to test ...

Dr. Jenkins: ... You're calling it an in-plant test in the truck. I don't understand that terminology. What's an in-plant test?

Dr. Spaulding: An in-plant test means that our veterinarian in the slaughter plant has the test capability. In the case of the calves in the ... test, we furnish them with cultures that are shelf stable, spore cultures. We furnish them with microbiological plate. We have furnished them with incubators, and a training guide.

And then we check a certain percent to see that they're on track, and by explaining what we've learned by explaining and working closely with industry in advance, industry supports these programs.

Dr. Jenkins: You said what I wanted to hear. You check periodically against your own standards.

Dr. Spaulding: Oh yes. We have to. We have our own quality controls and quality auditing systems.

Dr. Hoffsis: Precisely how is the sample obtained from these swine?

Dr. Spaulding: Right now, we're using urine, and when the hogs are eviscerated, the first thing they drop virtually is the bladder, and our people are collecting it.

We've got some problems in doing this. We're going to have to work with industry to figure out how to make it more efficient. We've stayed away from blood, primarily because it adds one or two hours and to the complexity because you have to deproponate the blood serum before you can use it.

These are questions that we're looking at, we're trying to improve. It's a matter of -- and this test is only good for a herd test. It's not good for an individual animal test.

And so there's a whole lot of these type of questions. But we're trying to match the program to the marketing system.

We did it with the cows, the ... cows. We did it with the calves, and now we're trying to do exactly the same thing with swine.

Dr. Schall: In the diagram that you had up there, the truck coming in, the only shortcoming I see there is that, quite frequently, that's ... hogs.

Dr. Spaulding: Oh, we know that.

Dr. Schall: You can't just put the pressure on the producer....

Dr. Spaulding: Oh, but I'm quite sure that the broker that represents in that truck will get the pressure put on him, and he will put the pressure on the producers.

Our law stops right at that packing plant. Our program is designed where we're totally legal. We'll be

working back through, you know, these other questions. The producers have been playing games with us for years, on this co-mingling, going to public auctions and all that. This program stops all that game playing.

I mean, quite frankly, it stops it. The fact that we just do one or two lots a day, and that's about all that we feel we have resources for, if you want to multiply that into numbers of hogs that would be retained on a given day, it gets frightening.

If you want to talk of yourself running a packing plant knowing that on any given day you could lose one or two lots that you had scheduled for kill, and try to, and you could be, either you have to pass the loss back to the supplier, or absorb it.

And you're talking in terms of losing the value of 40 to 200 hogs, if you want to run a business that way. I won't. I mean, quite frankly, I would not. I know about how I would collect my money.

Another thing that I think most of you gentlemen realize, that the packer will have these test results within the limits imposed by Packers and Stockyards Administration. We'll be working within the 24-hour window.

See, all these factors are going to come into play. We don know how, and quite frankly, we want to work with all people concerned, so that all of these questions are answered, and that's why we have a comment period that extends to August

30th.

Dr. Jenkins: Will be there be any form of pre-slaughter sampling? Are you going to collect feed or voided urine? Are you going to really go in and bleed?

Dr. Spaulding: We look at that. Those are options, when we talk about information supplied to the agency that indicate they're clean.

We know that if the feed is clean for a certain length of time, that we got clean hogs. We know that they can check urine or blood in ewes, say the sulfa slot test, and give us good results.

We'll be talking about those options with people, as to what they come to us with and say, this is the program that we can work with.

And we'll say, fine, here's where we'll establish the check point.

Dr. Anderson: Where would they get those tests run, State labs or ...?

Dr. Spaulding: The tests are simple enough that, again, we'd have to decide as to the credibility. I mean anywheres from -- I'm not quite sure, though I'm not opposed to it -- that producers could run their own, as long as they didn't lie...

And I happen to believe that 95, 98 percent of the producers are honest. I happen to think the other 2 to 5 percent, or whatever one you want, are the people that will cut

corners, if they were told that they could make more money by being..., and I think we've got that small minority out there -- I don't know how big it is -- but that small minority will cut corners, regardless.

And that's why I've never worried about whether I'll have a job or not.

Dr. Hoffsis: The antibiotics listed on one of your charts, with various categories, cattle and so forth, do you make any attempt or can you with the techniques that are used to distinguish between the various antibiotics?

Dr. Spaulding: Right now, we routinely -- see if I can remember them -- of course, we do chloramphenicol, but we don't even consider that in the category of antibiotics -- don't ask me why, but we don't.

We do penicillin, streptomycin, the three tetracyclines, erythromycin, neomycin. We have card tests and we've expanded to include tylosin. We have a card test for tylosin.

We have a card test for gentamicin. We've expanded into what we call an additional plate on our things that will not tell us which one or how much is there, but it will tell us if they are there.

We've added lincomycin, neomycin -- I can't think of the other two, but they're in the same family. We can tell that there's -- since we got a card test for neo, that just leaves three -- virginiamycin is one.

We do three more. We can't tell you whether, which one is there, but we can tell you that they aren't there, and from our standpoint, that's equally important.

Those are the ones that we routinely, except for the last three, we not only routinely identify, we quantitate very precisely.

Dr. Hoffsis: Can you tell which antibiotics are violated most often?

Dr. Spaulding: We have more problem with neomycin than any of the others because it does hang up in kidney, because kidney as a screen. You get streptomycin, instead of the penicillin, but you know it's really been treated with pen-strep ... I don't even know -- Jerry, can they even buy streptomycin alone anymore, do you know?

Dr. Guest: Not alone, no.

Dr. Spaulding: I doubt it. And so what you're talking about are those that hang up.

Incidentally, the STOP test and the CAST test cover a wider range of antibiotics than what we test for. They just lack the sensitivity. They're designed for certain sensitivity of a certain group.

It doesn't mean they ignore the rest of them. It just means the rest of them have got to be there in higher amounts. Like we don't claim our STOP test or CAST test touches chloramphenicol.

The reason is chloramphenicol has got to be there

about eight parts per million before we pick it up. It doesn't mean that it will miss it if it is ... It just means that ..., and that's not acceptable.

Dr. Hoffsis: Further questions. Dr. Guest, did you have a comment earlier?

Dr. Guest: Just one. I think, John, to be correct that the data that you see here were done with the traditional methods.

Dr. Spaulding: This is monitoring data.

Dr. Guest: Take a sample, send it into the lab...

Dr. Spaulding: ...It's unbiased. The data there, what I gave you on that chart is restricted. It can be only from normal, healthy animals. We cut out, because our inspectors are told to ignore the sick, and if they think they have to be treated, have been treated, they're supposed to retain and either test at the plant site or retain and send samples to the lab until we get the results.

So these are the normal, healthy, what we call normal, healthy. As you know, that includes a certain amount of disease.

Dr. Guest: My point was, what may not be clear to everybody is that the new test you're proposing will do lots more samples in a very short period of time, as compared to the way it's done today.

Dr. Spaulding: The estimate, we have 800 to 1,000 plants that kill swine. If we do two lots, 12 samples total at

at each plant, you're up past 1,000 samples with that. You're up to about 1,600 lots a day, and as I say, if you said any one of these samples of swine should represent an individual producer lot.

In other words, in a day, we'll be doing current testing, and we'll be doing it every day. And these are random, non-biased. We raise heck with our inspectors if they bias it in any way. And the other program's biased, based on knowledge of where the problems are.

Dr. Hoffsis: Further questions. Dr. Bechtel.

Dr. Bechtel: Could you comment on what's going on with the ... feed lot in ..., Oklahoma, or the quality assurance program.

Dr. Spaulding: I didn't get into cooperative residue programs deliberately, but if the group wants to hear about them, these to me are some of the most advanced and wonderful programs that we've got going.

It's just that we are suffering under a reluctance of he who is regulated to work closely with he who is doing the regulations.

And we're finding this mutually beneficial. We've had these programs of what we call cooperative residue programs -- I'm quite sure we're going to have to call them memoran;dums of understanding, or something, due to legal problems, but they're, in principle.

We've had them in the poultry industry. We've had

them, it started with Hitch. For your information, we just signed on at the Harris beef lot, and we haven't even told Harris yet. They sent one in, out in California.

But what they are is the company gives us and signs a legal contract that animals produced under their management will meet all the residue claims, and furthermore, that they will use no drugs that are not legal from an FDA standpoint.

Now this includes the veterinary-client relationship. But if they do that, they run tests, so that when the animals come to slaughter using current test technology, they're negative, and we check them then when they come in.

As part of this agreement, not only has the company agreed to do that, they lay out in writing how they're going to accopmplish it, and furthermore, invite us to come and visit their place of operations at least once a year. It's really an open invitation, but at least once a year, to verify they are following and keeping the records required.

The sick pen animals come to slaughter with treatment cards, so that because they're segregated normally, they're working together, and it's a cooperative effort between a regulatory agency that does the inspection and the companies that are producing animals.

And the thing is that we can, as our agency is exploring, but what we will be able to do is allow them to even go as far as to make label things based on these programs.

Dr. Bechtel: There have been some inquiries in our

area. They're wanting to do more and more of that. How do we get this started? We were told by one ... they were just going to have this pilot program....

Dr. Spaulding: No, we're going beyond Hitch. Now the, again because of the restrictions on our program. We have to have a packing plant involved, because that's the only place that we can sign the, you know, this type of an agreement. So we have to have a slaughter plant. Plus the agreement wouldn't be very good without a slaughter plant.

The thing is then through the slaughter plant we can work with the producers and work out exactly the same program as what we have with Hitch, and the same agreements.

Now we will check them. We set up their animals so that we are checking on a regular basis. They go out of the normal monitoring program, and they go into special sampling, so that we look for, and check them periodically about once a month, once a year, depending on their volume, again.

And one of the things that we look at is how much further can we go in working through the packer back to the feed lot, because we're looking at that right now, and I haven't quite got money transferred over to ERS so that I can talk about those programs, and they haven't got the agreement signed with the universities.

In effect, Doug Marr and Dee Griffith have the type of program I'm talking with already working on Hitch animals.

Doug Marr is our veterinarian at the plant where

Hitch slaughters about 25, 30 percent of their cattle, and Dee Griffith is the veterinary consultant at Hitch. And they're two horse people. And so, really, when Dee wants his animals checked for some special treatment, he just tells Doug, Doug, would you look at the next lot coming in? And then Doug informally tells Dee what he saw.

And it has improved their overall management. Dr. Bechtel, you're closer to them than I am, but I think that's improved the treatment regimes and all that at Hitch even more.

Dr. Bechtel: Well, this is back to the old positive thinking again, and rather than talk about..., we want to talk about quality assurance, and we've got Texas Cattle Feeders Association and several....

Dr. Spaulding: What we'll do is anything, I mean, to answer to what you can tell your feeders, we'll do anything that we can to work out a program. They tell us the circumstances and we'll sit down with them, and tell them, OK, legally this is how we can get to you.

In the Hitch, it's unusual, is that we are actually working with six or seven slaughter plants. In other words, we are not trying to restrict their marketing or anything..., and Hitch happens to own some slaughter plants, so we can directly deal with them.

But we are not saying it's only a, covers ... animals in your two slaughter plants. We're saying anyplace you sell

cattle, we will accept.

And it was pilot, but we're so happy with it, and Harris came in with a direct typical -- what I call typical -- poultry operation, and we just finished working one out with them.

Again, we do not tell the people how they have to do it. We check what they say they're doing to see if it accomplishes the end purpose.

Dr. Hoffsis: Further questions or comments? Thank you very much, Dr. Spaulding, and at this point, I think we will take about a 15-minute break.

[Break]

Dr. Hoffsis: This time I'd like to introduce Dr. Van Houweling, who represents the National Pork Producers Council, serves as a consultant to other groups, and is the former director of the, what used to be the Bureau of Veterinary Medicine, FDA, and our Committee has asked him if he would serve in essentially an advisory role to the Committee, or a consulting role to the Committee on various issues including the sulfa residue problem, and we've asked him if he would give us the benefit of his experience and for additional background purposes about sulfa residues in swine today.

Dr. Van Houweling.

Dr. Van Houweling: Thank you very much, Chairman Hoffsis.

Members of the Committee, ladies and gentleman and

former associates. You noticed I said ladies and gentlemen first.

It's nice to see you, a lot of people I don't see very often anymore. It's good to see a number of people that I had the pleasure of working with for a good number of years.

I'd like to compliment the Committee, too, for the important job you have, and thanks to all of you for doing ... take the time to serve, because it is time-consuming.

I remember we once had an advisory committee and we put people through the same kind of thing that you're doing. It lasts a day and a half or so of this kind of thing, off and on, and we certainly used advisory committees a lot when we were studying antibiotics in animal feed.

I don't know how many committees Gerry Guest had altogether, but we had quite a few, didn't we, Gerry?

Dr. Guest: Yeah.

Dr. Van Houweling: One, I think I had one task force that functioned almost for two years, didn't it, Gerry? A 15-member task force, but it functioned for almost two years on the antibiotics in animal feed.

We had a little difficulty reaching a consensus sometimes ... as you can imagine, with 15 people on the subject of low-level antibiotics in animal feed.

We finally came out with a report -- it didn't make any difference whether we did or not -- but we did come out with a report, and we've led to another study.

So that's the way it goes. So I hope your Committee will be more effective in that. ..., if I may, gentlemen, maybe before I talk about sulfas, I think I ought to mention chloramphenicol in swine.

About a year ago, the NPPC was made aware of the fact that you could still use chloramphenicol in Canada, albeit on a prescription from a veterinarian, in food animals.

At that time, we wrote a letter to the USDA and said, you know, we thought that was questionable practice, since there were so many hogs and so much pork coming in from Canada, and the FDA was taking a current position that this couldn't possibly be used in food animals in the United States.

Well, it didn't have much impact on the USDA, and about all we got was assurances that they were studying the problem, and Canada was going to do something about this sometime.

This went on, actually, until just the other day. Canada finally announced that they have proposed to withdraw the use of chloramphenicol in food animals -- 60-day comment period, similar to our, it's a drug, ... letter they call it there...

?: Information letter.

Dr. Van Houweling: Information letter. But that's still... And so they're going to be studying it for 60 more days to determine whether or not they should go ahead with their proposal to ban, ... to use that word, the use

of chloramphenicol in food animals.

I understand that USDA has done some testing for chloramphenicol in imported products and haven't found any, though Les ... and Lester Crawford says that the tests we have really aren't that effective because they are for the intact substance, and in most cases, we'd be looking for a metabolite, providing the hogs have gone through the marketing channels and are slaughtered.

And they probably do not have an effective method for the metabolite which we should be looking for at the time the hogs are slaughtered.

So I'm not sure how important it is if USDA has tested, I believe, 650 hogs that came in from Canada. But at least that's the up to date on that.

Now, I'm moving to the sulfa residue. You've heard so much about it already that I hesitate to talk to you about it anymore.

But let me just give you a little bit more background and maybe a little different point of view on some points.

I can remember very well when the FSIS came over to FDA in the '70s, during the '70s, and said there is a definite problem with sulfa residues in swine and in turkey. They were both found to be much higher than they though they should.

With that, FDA intensified their premises inspection. As Gary said earlier, too often it's some weeks before the FDA inspector actually gets to the premise.

FSIS, in fact, I think it was the Food Quality Safety Program, had a program whereby if a man shipped hogs to a packing plant and they were testing it and found it had violative residues, he could not market any more hogs until he had sent five additional animals that were free of residue.

And that program led to a great deal of difficulty and consternation and loss in the pork producers, who had a great big meeting downtown one time. There was 250 people there, I guess, in which we had this debated vigorously, and producers were there and telling their tales of woe.

One man from ..., Iowa, had an ... herd, and he did not feed any sulfa whatsoever in his feed, and still he was one of those who was found to have violative residues, and he was one of those who had, you know, 50 or 100 hogs that had to go to market every week. They just, the pens get full. They got to go someplace, and he couldn't move them.

He took tremendous loss. Of course, marketing of those hogs, ... and heavier and so forth. I think they finally worked out agreement that they sacrificed the livers, and he got docked pretty heavily.

There were other tales like that, and all it has an effect on them. They're a little skeptical, you know. That's questionable, that kind of stuff.

What went on then, when the enforcement activities really didn't produce any results, and they didn't. That darned level just stayed up there, about 12, 13, up as high as

14 percent. Dr. Moen was then the head of, I believe it was then called ARS. That was back there in the old day. And Dr. Moen was at a Secretary of Agriculture staff meeting, and they were talking about their great problems with the enforcement.

And Frank was wise enough to say at that staff meeting, "Why don't we see if we can help these people solve this problem, instead of just enforcing the law and beating on it?"

And that struck a responsive note with the Secretary. They were given a million dollars, which they scattered out through research programs, the Extension Service, and APS.

And they all went to work with the producer trying to find out just what did cause some of these problems. There was a ... done with feed mills, how much carryover there was in feed mills, and so forth.

And they came up with a lot of good information, which they got out very rapidly, and it led to this sharp reduction.

If I could have that first transparency, Jerry. I'd just like to show you -- this is data, as John said, came from his files. A little different from what he showed you, but you see in '74 and '75, there was about nine and a half or nine percent.

It jumped as high as 13, but then when you see the educational program went into effect about in '77, and you can

see the marked reduction we achieved, down to around 4.3 to 4 percent.

Unfortunately, as they pointed out, it started to climb again in '82, and it has climbed to about six and a half percent in '84.

Now I put the violative residues on turkeys, because you see, we called it to their attention in '75, and they were able to achieve a marked reduction very promptly. I don't know why there was that little increase in '78 and '79, but you see now the turkeys are running in the acceptable range of one to two percent.

We've been aware of this increase -- you can turn it off now -- we've been aware of this increase for over a year. As Gerry and John both pointed out, they made us aware of it, made the industry aware of it.

We've had those meetings that they talked about, and the Pork Producers have really tried very hard to carry an informational story out to the producers.

I think I assembled for that meeting we had with Commissioner Young 14 examples of material that we had sent out over the year to producers in regard to the need for doing something about the sulfa residues again.

I have, the trade press has been helpful. I have, here's one example, I believe I have enough copies here for the Committee. This is a pretty good summary that was published in Feed Stuff, or in the National Hog Farm. You can pass

these down the line.

But this is rather typical of the kind of material that's been going out. Here's one of our stories. Here's another Feed Stuff story. Feed Stuff does an excellent job of bringing these things to the attention of producers. I guess you can see that.

Here's another one of our stories, and we have letters going out to industry leaders, and we've been stressing this need for attention again to the sulfa residue problem.

The FSIS is develop an excellent slide show, and this booklet to go with it. They've been sent to all the State Extension Services, to all the State pork associations.

So there's been a tremendous effort gone in, to train, to inform producers.

The latest effort really is a matter of the check stuffers. Don't keep those, but just pass them around. We have developed -- you can look at them -- we developed eight different check stuffers now, or envelope stuffers, that are going to be distributed by feed companies and ... companies, as well as all our marketing companies. Everybody that buys hogs is going to have a chance to...

So that's the latest effort ... really just gotten around, and so I don't know if they'll have any more effect than what we've done up to now.

But what I'm trying to say is that they certainly have been made aware of the problem. We certainly have been

trying to work on it, I must say. We've had excellent cooperation from the agencies.

And producers are concerned. There's no questions about that. Maybe a producer doesn't get really concerned until he's hit with a regulatory action as an individual.

But, in general, producers are very concerned. They're concerned about this whole matter of the safety of food. We lump it together into the diet-health consideration.

Cholesterol, drug residue, pesticides, fat is all in one general topic, and it has had its effect on the consumption of red meat. There's no questions about it, and this gives the usage of red meat reconfirmed.

And the next slide, Gerry, I brought along with, just to show you how this red meat consumption has changed, compared to the consumption of chicken.

This one estimate, USDA says that chicken consumption '85 will reach pork, and you can see how the lines have been going together.

In other words, they're predicting that chicken consumption will be in the neighborhood of 58.6 pounds, which will be about the same as pork consumption this year.

The next one, Gerry, is a similar slide, but it's all on the basis of percentage of the market. And look at 1940, chicken, compared to 1984. Beef at 1940, '80 and '84, it's been going down some, too. It had a slight raise, but look what's happened again to pork consumption.

Now this really does concern producers a great deal, because, as I say, they feel like this matter of residue, diet and health is all one big package, and for some reason or other, people are eating less red meat.

To confirm this, we had the National Livestock and Meat Board, which, as most of you know probably, is a organization that works with producer parties to, market products, I guess that's the way to put it.

They conducted a survey of consumers in the latter part of '84 and beginning of '85 in regard to their awareness of the antibiotic issue.

Well, they found out that unaided, that is, before you tell anybody about it, less than two percent of the people were concerned about antibiotics, and low-level antibiotics.

Once they discussed low-level antibiotics and told them something about it, then 60 percent became concerned, just slightly less than those that are concerned about chemical residue and pesticides.

And fat and cholesterol, all in that same area. So producers have the feeling that this whole thing is one big problem, and if residues contribute to the problem, they certainly want to try to eliminate any concern.

We had a meeting, let's see, the latter part of April -- wasn't it, Gerry? -- with Commissioner Young -- I think Les happened to be out of town, or out of the country -- with Commissioner Young and Dr. Guest, and also

Dr. Houston of the FSIS.

I tried to express to them my real concern about this, and what we've been doing to try to inform producers the need for something more to be done than they've been doing.

I guess our basic plea was give us a little bit more time, but we were a little late because the balls were already rolling.

The FSIS inspection letter had gone out, which I haven't heard a bit of criticism of the letter, incidentally, Dr. Crawford.

Dr. Crawford: What?

Dr. Van Houweling: Hadn't heard any criticism of it so far. I haven't heard much one way or the other.

Dr. Crawford: That's because all 114,000 pork producers had something to do with writing the letter.

Dr. Van Houweling: Not quite. I could say there was a couple of changes in it I suggested that you did not incorporate.

[Laughter]

Dr. Crawford: Dr. Van Houweling, after we incorporated 305 changes, I mean, surely you can give us two.

Dr. Van Houweling: Gerry was assuring everybody that all suggestions were incorporated.

Dr. Crawford: That's the way he is.

Dr. Van Houweling: But the FSIS told us at that time that they had this program that Dr. Spaulding discussed, and Notice of Intent to Regulate also was well underway and would

be out any day.

So, it looks like the ball is rolling for more enforcement again, and I'm just not sure that more enforcement is going to do any more than it did in 1975, 1976, 1977.

It may be that's the only way to get producers' attention. It will get the attenion of those that are affected, are inspected.

They really worry about having the FDA inspector come on the farms. They tell me those fellows aren't helpful at all. They don't know anything about raising hogs. And I said, well, that isn't their job. They really aren't there as extension people, they're out there as inspectors ..., so don't expect them to be helpful.

I don't know, I'm not going to try to comment on John's program ... I think that's going to be subject to an awful lot of comment, and before August 30, when the comments are due, I'm sure that you'll hear from a lot of people about that, because that is, as he indicated, a very, I guess you'd say, disruptive possibility in the marketing and slaughtering of animals if that's carried out.

We had at every meeting, and I think it's worth mentioning, we were responsible for getting together a number of the principals that were involved in 1977 in this program. They're still around town, fortunately.

So we got together and we sat down, what did we do in '78 and -- yeah, '77 to '78?

What's different now than what we had then? And trying to examine whether or not there were some things we had overlooked in our educational effort that we could utlize.

Somebody mentioned the work at Purdue, and, Jerry, if you don't mind putting that fourth one on, I think that the residue avoidance program ... it's carried out, and that the FSIS fund it. They went on for two or three years, did a lot of good work.

This is one page of the report from the Purdue study that Dr. Foster and a couple of associates carried out in Indiana where they inspected 80, I think it was 81 or 82 swine producing establishments, and they went back to them a second time.

But the four factors that they associated with cross contamination or withdrawal feed, you see, are the type of sulfonamides that went back to the powdered sulfas.

They found that it was being fed at levels much higher than for which it was approved, two and three times. If you do that, your ... is naturally greater because there's more contamination ...

This percentage of medicated feed again, how much of the total feed left on the farm was medicated.

It makes a lot of difference whether you're just feeding it for a group of ... pigs, or whether he's feeding sulfa right on through to ...

And they found that the producers were not as careful

about sequencing, flushing and cleansing -- I don't know if those words are familiar to your folks, but sequencing is primarily mixing drugs with the lesser concentration of drug as you go towards the withdrawal feed, so there's less in danger of contamination as you go down the line.

And the commercial mills do that very well, and I think this is something the on-the-farm mixers have to learn to do, too.

Now, this bottom chart, this Table 2, shows very well that the powdered sulfa is a factor. The residue risk for it worked out is, was based on all the factors they could observe, and you can see that for the powdered, the residue risk on the first visit was more than twice as high as if they were using granulated.

And for some reason, I guess we know why, sulfathiazone doesn't seem to be a problem.

But, there's no questions that we have some more information about some of these things than we had in 1978, when we started the other programs.

A couple of other things that we find that we could agree on that differ. Commercial feeds, I think, are less.... They, the feed mills, have probably almost all gone to the granulated product. They are probably doing a better job of sequencing and flushing than you would ..., if necessary.

So I think commercial feeds -- the sale of powdered sulfa was not a factor back then because there wasn't any

granulated available until about '79. So it was all powder. So that is a factor that's different then and now.

I believe, though, that the availability of the powdered sulfa for other uses is still a big factor, because if a fella has used the powdered sulfa in drinking waters, he's found it works. And if he can buy it, and he can add it to feed, I think there's naturally quite a temptation, and it may be a temptation on the part of some people to sell it to them for use in feeds, and it was not sold for that use.

I know of one producer, and I won't give you his name, who tells me he buys the powdered sulfa from his practicing veterinarian. So there are some practicing veterinarians out there that take to selling powdered sulfa, too.

There is, of course, more on-the-farm mixing all the time. There is less commercially mixed feed being sold, but that's the other factor. There's more on-the-farm mixing.

And there is the indication from John's residue there, more detail than you saw, that the older animals, the... breeding stock, the sows and the boars, are the biggest source of residue when they're sampling.

And maybe if the ... have withdrawal periods for those animals, too, before they go to slaughter. They would be staying on feed and were not as carefully withdrawn as the other market animals.

Well, where do we go from here? We, of course, are

going to be looking for more reports from the kinds that FDA expects that Gary referred to.

If I understood him correctly, he was only able to trace back two of sample reports. Is that what he said?

Dr. Crawford: Correct.

Dr. Van Houweling: That's discouraging.

Dr. Crawford: We can only trace back about 20 percent of them, at best.

Dr. Van Houweling: You'll have to have a lot of reports if you're going to get very many....

What your inspectors learn on that program that is very useful information, as I indicated already, that the FSIS publication that John referred to is going to get a lot of discussion, I can assure you, and it's not going to be just the swine producers. It's going to be the meat packers and the marketing companies as well, because this could be quite a disruptive influence ... market.

So, I guess we still feel that with the intensified educational programs, there is a chance that we can reduce the level of violative residue, and so that the FSIS program may not be necessary. We hope we can.

And we're going to be continuing to work with all the group to see if we can't get some more reduction in the violative level in the months ahead.

So, Mr. Chairman, thank you very much for inviting me. I'm glad to be here, and if there are some questions that

I could answer, I'll be glad to try to.

Dr. Hoffsis: Well, we're very glad to have you. Appreciate your comments. Are there some questions for Dr. Van Houweling?

Dr. Lassiter: In that last statement, Don, you made about the sows and boars, that the residue levels are higher -- significantly higher?

Dr. Van Houweling: Yeah, very much so.

Dr. Lassiter: I see. That might be an important educational program.

Dr. Van Houweling: May not be important...?

Dr. Lassiter: I say, that point may be important in an educational program... Our data is solid here?

Dr. Van Houweling: Well, John's got, he's got very good data on the, and in those older animals the residues are much higher. The level is much higher, which indicates that they may have been fed medicated feed almost right up to the time they were slaughtered.

Dr. Lassiter: ...used to be, can't hold them either. I mean they just decide they're going to sell a sow today, and off she goes. That's probably what's going on.

Dr. Van Houweling: I guess that's true, too. They don't have that period, they don't know in advance.

Dr. Lassiter: Whereas with market hogs, they know they've got to take them off feed, see, but they just ship the old sow to market.

Dr. Van Houweling: One thing about on-the-farm tests, John says they haven't learned how to collect urine of in the antemortem pen, and that's a little bit of a problem on a farm, too, in fact. Fellas that raise pigs tell me if you get out there in the morning when the hogs get up, you can get quite a little of itl, because the first time they get up they probably urinate, but after that, it's not easy to get urine out of a pig.

So I don't think they ought to be too disappointed if farmers don't use that urine test in... Yes.

Dr. Jenkins: I wondered, Dr. Van Houweling, what the, what would the penalty be for a violator if someone is found to be in violation.

What's the next step? Do the producers to anything? Or is it entirely from the regulatory standpoint.

Dr. Van Houweling: You see, Dr. Jenkins, when they have had programs that you can't market any hogs until you send five days clear on it, that was a very significant penalty.

They maintain that quality has never changed, but I haven't talked to a producer in the last several years that ... any hogs out of there, so I don't think they've been doing that for a while.

Dr. Spaulding: Don, we have been, but there's a factor of numbers of producers affected. When you're just affecting five or six producers across the country, you really don't get much reaction.

When you jump the sampling rate up to -- you know, leave percentages the same, jump the sampling rate, you get more producers. Then they start talking, and that's when you start -- and also the packers get more interested. Instead of one producer a month, now they've got 10 producers a month, and it also intensifies the programs.

And I agree with Don that until we got an educational program going, we really weren't affecting the violation rate, but we sure got them interested.

Dr. Jenkins: So the punitive measures actually come from the regulatory agency. The law enforcement doesn't get involved there at all, even though it is, in fact, breaking the law.

Dr. Van Houweling: Doctor, let me say that I asked Gary Dykstra at a meeting in St. Paul. He said there were two possible actions you could take after you found in an inspection, you found somebody guilty of illegal practices or....

I said what are they? He said, one is a regulatory letter, and the other one, he said, an injunction against market.

Now I don't know whether he really checked that out or whether you folks have thought that true.

That would be a possibility, to enjoin anybody from marketing more animals.

Dr. Crawford: There are all sorts of strategies that

could be taken. What Gary referred to is that for an initial violator, it's just a regulatory letter, but you know you build a case of whether or not they are a repeat violator and so forth.

If it becomes clear that they're intending to adulterate the meat supply, then you have to go to the courts and try to seek the most direct way to keep whatever it is they're producing out of the food chain. Injunction's a possibility.

Dr. Van Houweling: And you did get that done for veal up in New York.

Dr. Crawford: The DES veal calves in New York. We had a ... of veal calves for longer than we wanted.

Dr. Van Houweling: There's one other thing that the Committee might consider in this regard, Les, is that matter of your work at Pine Bluff.

Dr. Crawford: Um hum.

Dr. Van Houweling: If John's agency takes you out of action on one-tenth of a part per million, just a couple of years from now, you'll say, whoops, it wasn't necessary to be one-tenth, but the liver could have been three-tenths, because that is your policy now if it's not carcinogenic.

That will have a disastrous effect as far as the industry is concerned. Unless you're at the nitrite program, which the agency said had to be banned, and then two years later said, oops, we made a mistake, it isn't necessary, after

all. I hope we don't have the same thing happen in our sulfa residues again. I think that would have a disastrous effect.

Dr. Crawford: Well, we're monitoring the results, as you know, and, so, when we have tentative reports, we'll keep everybody informed as the first ones of those become available, but we don't know yet.

We have every expectation that it will be completed in early '86.

Dr. Van Houweling: That might be soon enough.

Dr. Crawford: Um hum.

Dr. Hoffsis: And on that point, that study is to look at this action level of a tenth part per million?

Dr. Crawford: No, it's to determine, once and for all, whether or not sulfamethazine is carcinogenic, or if it's thyroid active at the levels you would expect.

So, the best eventuality for those that have advised an elevation of the action level, is that it's proved to not be carcinogenic, nor have any effect on the thyroid gland.

In that case, it would be possible that you could raise the action level. The other thing that could happen is that if it has an effect on the thyroid gland at levels ... or if it's carcinogenic, then it likely would have to come off the market. That would be the other extreme.

These studies generally fall somewhere in the middle, though.

Dr. Phemister: Is the thyroid effect being measured

in NCPR, too?

Dr. Crawford: Um hum.

Dr. Phemister: In what species?

Dr. Crawford: Rats and mice.

Dr. Hoffsis: Are all of, the only problem currently is with sulfamethazine, right?

Dr. Van Houweling: ...(unintelligible)...

Dr. Hoffsis: And the, all of the approvals, the approved combinations, are for sulfamethazine?

Dr. Crawford: No. Sulfathiozol is also approved.

Dr. Hoffsis: And the ramifications there of just switching forms of sulfa are, what? I mean is the...

Dr. Van Houweling: Well, the producers just haven't become convinced that sulfathiozol is as good. According to the FDA measurements, as I recall, I think it did just about the same thing, as far as growth promotion and feed efficiency are concerned. What we were discussing at lunch, you know, how well the user can evaluate the effectiveness of products. I would think... there's no reason why sulfathiozol shouldn't be as good, but it's never sold as well.

Now, maybe that's all just advertising.

Dr. Crawford: Our only role in that is to show that they're both safe and effective, which we've done, and what the marketplace does to discriminate, we are not involved in.

Dr. Hoffsis: Further points. And thank you very much, Dr. Van Houweling. Are there other comments from the

audience on any subjects of today.

We are finishing a little early, and Dr. Crandall has mentioned to me that there is a 10-minute presentation about the Center that they might show just for our own information, if we did have the time.

So, since we have the time, we will see that at this point.

[Recorded presentation]

Dr. Hoffsis: Very good, Max.

Dr. Crandall: That is it, you know, we had the cartoons and everything first, and then we just had the main feature.

Dr. Hoffsis: That's an up-do-date film.

Mr. Schrivener: We just got that, just finished it about a month ago.

Dr. Hoffsis: Do you have any announcements, Bert?

Mr. Schrivener: Eight o'clock tomorrow morning, is it?

Dr. Hoffsis: We begin at 8:15, tomorrow morning.

Mr. Schrivener: We will try to have everyone out by noon.

Dr. Hoffsis: We will adjourn until 8:15.